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SUMMARY

This Adverse Drug Experience (ADE) inspection of sanofi-aventis US LLC, the US affiliate for sanofi-aventis, Paris, France, was initiated per HFD-332 request (FACTS assignment # 1139577, OP ID 4601211). CP 7353.001, Enforcement of the Postmarketing Adverse Drug Experience (PADE) Reporting Regulations, was used as inspectional guidance.

The previous inspection of this firm covered medical devices, was conducted from August 24 to September 3, 2009, and was classified VAI. The last ADE inspection of this firm was conducted from May 25 to June 8, 2006 and was classified NAI. That inspection was done at the previous location, 300 Somerset Corporate Blvd., Bridgewater, NJ, under a different FEI number (3004948112). Its focus was on the submission of ADEs for liver toxicities and follow-up activities involving Arava and Ketek. A PADE inspection of the firm's Global Pharmacovigilance & Epidemiology site in Chilly Mazarin, France was conducted from June 2 to 5, 2009 and was classified NAI.

Inspectional coverage included processing and submission of ADEs, periodic (aka aggregate) safety reports, and NDA Annual Reports. Periodic safety and NDA Annual Reports, as applicable, were reviewed for these products: Ambien (NDA 19-908), Apidra (NDA 21-629), Elitek (BLA 103946), Eloxatin for Injection (NDA 21-492), Eloxatin Injection (NDA 21-759), Ketek (NDA 21-144), Multaq (NDA 22-425), and Oforta (NDA 22-273). The US affiliate is responsible for processing all spontaneous ADEs received in the US, preparation of US Periodic Adverse Drug Experience Reports (PADERs) and NDA Annual Reports, and a small number of clinical study cases. All foreign reports, the vast majority of clinical study cases, and Periodic Safety Update Reports (PSURs) are the responsibility of the company's Global Pharmacovigilance & Epidemiology (GPE) departments. GPE is located at another facility in Bridgewater, NJ and also in Chilly Mazarin, France. The US affiliate is responsible for determining the expectedness (aka listedness) for all ADEs reported to the FDA against the US label, whether from domestic or foreign sources. All submissions to the NDA are done by US Regulatory Affairs Marketed Products staff at this location.

Inspection disclosed that not all ongoing postmarketing studies had been included in NDA Annual Reports for Apidra, Elitek, Eloxatin and Ketek. In addition, other clinical studies that were either ongoing or completed were reported late to the NDA Annual Reports for Ambien, Apidra, and Eloxatin. They were mainly foreign studies. Although they were not postmarketing safety commitments, the firm acknowledged that two Eloxatin studies reported late were safety studies. Around April 2008, the firm started retrospective reporting of clinical trials that were not previously reported to NDA Annual Reports as safety studies or postmarketing study commitments and/or to the IND. The firm stated that this was initiated following issuance of a warning letter to another pharmaceutical company for not reporting clinical studies to their NDA Annual Reports. Previously their understanding was that only postmarketing study commitments or safety studies had to be included in NDA Annual Reports and that IND studies were submitted to the IND Annual Reports.

There were about 185 initial 15-day reports that were submitted late for the time period of January 1, 2009 to March 31, 2010. Approximately 22% of these late 15-day reports were at least 30 days late. An estimated 127 15-day follow-up reports were submitted late during this same time period and about 35% of these were at least 30 days late. 8846 initial and follow-up 15-day reports were submitted to FDA during this time period with around 3.5% being reported late. Approximately 60% of all late 15-day reports were foreign reports.

On November 9, 2009, the firm started utilizing [redacted] (b) (4) [redacted] AE Reporting System (AERS) for data entry, coding, tracking and reporting individual case safety reports (ICSRs). This system is also used for adverse events associated with medical devices. Use of their two legacy pre-merger software systems, [redacted] (b) (4) and [redacted] was stopped. In November 2009, about 12% of ICSRs submitted to FDA were late. By April 2010, the number of late ICSRs decreased to 3.8%.

Other inspection findings involving GPE responsibilities, not listed on the FDA 483, related to incomplete information in clinical study tracking databases, release of the [redacted] (b) (4) system into production by an Interim Validation Report with multiple deferred issues, and inclusion of clinical studies in PSURs. Both the [redacted] (b) (4) Validation Report and the associated Traceability Matrix had not been finalized by GPE, the global unit responsible for the testing.

The firm's management was cooperative and stated that they would submit a written response to the FDA 483. Changes were made to procedural documents during the inspection. In addition, corrective action plans were provided for a compliance monitoring plan to identify late 15-day reports and the clinical study tracking databases prior to the completion of the inspection.

ADMINISTRATIVE DATA

Inspected firm:	sanofi - aventis US LLC
Location:	55 Corporate Drive Bridgewater, NJ 08807
Phone:	908-231-4000
FAX:	908-981-7894
Mailing address:	PO Box 5925 Bridgewater, NJ 08807
Dates of inspection:	4/6/2010, 4/7/2010, 4/9/2010, 4/12/2010, 4/13/2010, 4/15/2010, 4/16/2010, 4/21/2010, 4/22/2010, 4/26/2010, 4/29/2010, 4/30/2010, 5/3/2010, 5/4/2010, 5/7/2010, 5/13/2010
Days in the facility:	16
Participants:	D. Jeanne Denes, Investigator

On April 6, 2010, I (Investigator D. Jeanne Denes) presented my credentials and issued a Form FDA 482, Notice of Inspection, to Barbara Rullo, MD, Vice President, Drug Safety. She stated that the name of the firm was sanofi-aventis US. Dr. Rullo said that she was the most responsible person at this location for pharmacovigilance (PV) and authorized by the firm's management to receive the FDA 482. At the conclusion of the inspection, a Form FDA 483 was issued to Paul H. Chew, MD, US Chief Science Officer/Chief Medical Officer, for sanofi-aventis US LLC, the most responsible person available at the US affiliate.

HISTORY

sanofi-aventis is a global company headquartered in Paris, France. Its corporate headquarters are located at 174, avenue de France, 75013, Paris, France. At the end of 2009, it had approximately (b) (4) employees worldwide and a presence in more than 110 countries. Sanofi-Synthelabo acquired Aventis in 2004 and the name of the firm became sanofi-aventis. Legacy companies include Sterling-Winthrop, Hoechst, Roussel, Marion Merrell Dow, Rhone Poulenc, Dermik Laboratories, Rorer and Fison. Other companies recently acquired by sanofi-aventis are Merial, an animal health company, and Chattem, a US consumer healthcare company. Sections of the firm's 2009 Annual Report are attached as Exhibits 1 and 2.

sanofi-aventis US LLC is the US affiliate of sanofi-aventis and was incorporated in the state of Delaware in 2005. This location (55 Corporate Drive, Bridgewater, NJ) is the corporate headquarters for sanofi-aventis US LLC. There are about (b) (4) employees at this site. The firm still maintains some offices at 300 Somerset Corporate Blvd., Bridgewater, NJ (FEI 3004948112). Office hours are 8:30 am to 5 pm. However, many employees work a compressed work schedule Monday to Thursday and not Friday afternoon.

sanofi-aventis has approximately (b) (4) employees in the US including the sales force. There are four pharmaceutical research sites in the US located in Bridgewater, NJ, Malvern, PA, Cambridge, MA and Tucson, AZ. The R & D division of sanofi-aventis has laboratory and other facilities at 1041 Route 202-206, Bridgewater, NJ 08807. Global Pharmacovigilance & Epidemiology has offices at 200 Crossing Blvd, Bridgewater, NJ. The US Clinical Research Unit Site is responsible for IND submissions to the FDA and is located at 9 Great Valley Parkway, Malvern, PA 19355.

Vaccines are also manufactured and marketed by sanofi-aventis. The US sanofi pasteur facility is located in Swiftwater, PA. In March 2010, sanofi-aventis purchased Chattem, Inc., Chattanooga, TN. Chattem is a manufacturer and marketer of consumer healthcare products including over-the-counter (OTC) drug products. sanofi-aventis US LLC is not responsible for handling any product complaints or adverse drug experiences for either sanofi pasteur or Chattem. Both sanofi pasteur and Chattem have separate pharmacovigilance operations that are independent from the sanofi-aventis US LLC, Drug Safety Department, and sanofi-aventis GPE. They have their own safety databases.

All regulatory correspondence related to this inspection should be addressed to Gregory Irace, President and Chief Executive Officer (CEO), sanofi-aventis US LLC at 55 Corporate Drive, P.O. Box 5925, Bridgewater, NJ 08807-5925 with a copy to Barbara Rullo, MD, Vice President, Drug Safety, at the same address.

INTERSTATE COMMERCE/JURISDICTION

sanofi-aventis annual global sales for 2009 were approximately (b) (4) Euros or (b) (4) US dollars. There are no manufacturing, laboratory or distribution operations at this location. US distribution centers are located in (b) (4)

The majority of the products marketed by this firm are pharmaceuticals. Other products include Drisdol (a dietary supplement), two medical devices (Hyalgan and Sculptra), and two cosmetic products (M-Professional Revitalizing Peel and Shepards Cream Lotion). All NDA, ANDA and the BLA products marketed in the US are held by the US affiliate, sanofi aventis US LLC. There is one over-the-counter (OTC) monograph drug product, not covered by a NDA. This is Zephiran Chloride (benzalkonium topical solution). The firm's product listing with applicable approval numbers is attached as Exhibit 3. The list of products where the sanofi-aventis name is on the label is attached as Exhibit 4. A product list was also provided indicating the Global Pharmacovigilance & Epidemiology (GPE) site assigned to each product worldwide. It is attached as Exhibit 5. The GPE product assignment list for US marketed products was provided during the June 2009 inspection of sanofi-aventis in France. See Attachment 5. Three NDAs were withdrawn by sanofi-aventis and were published in the Federal Register in February 2009. See Exhibit 6.

Current US Package Inserts for Ambien, Apidra, Elitek, Eloxatin, Ketek, Multaq, and Oforta are attached as Exhibits 7 to 11.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

At the beginning of the inspection, I presented my credentials and issued a Form FDA 482, Notice of Inspection, to Barbara Rullo, MD, Vice President, Drug Safety, who said that she was the most responsible person for pharmacovigilance at this firm, the US affiliate. Dr. Rullo facilitated the inspection with the assistance of her staff. She participated in daily wrap-up meetings as well as the closeout meeting at the end of the inspection.

The following are personnel from sanofi-aventis US LLC involved during the course of the inspection:

Craig M. Audet, Vice President, US Regulatory Affairs Marketed Products (US RAMP)

Mr. Audet provided information regarding the firm's procedures for NDA Annual Reports, the retrospective reporting of clinical studies to NDA Annual Reports, and postmarketing commitments. He participated in some daily wrap-up meetings and also in the closeout meeting at the conclusion of the inspection. His signature appears on SOP US-EG-007 v02, NDA Annual Reports, as one of the approvers. See Exhibit 19, page 2. He reports to Paul Chew, MD, US Chief Science Officer/Chief Medical Officer. The Organizational Chart for US Medical Affairs indicates this reporting structure. See Exhibit 14, page 3. Mr. Audet's staff includes the Regulatory Submissions group responsible for the preparation of NDA Annual Reports as well as three therapeutically aligned Regulatory Affairs groups. See Exhibit 12.

Rosalina (Rose) Domin, Senior Director, Case Management, US Pharmacovigilance

Ms. Domin provided information on processing of cases and periodic safety reports. She accompanied me while her staff demonstrated the flow of cases. Activities performed by the Case Management group include monitoring of the company's call center database for ADEs, the triage and data entry of individual case safety reports (ICSRs) into the safety database, follow-up of ADEs for additional information, assessing ICSRs for seriousness, preparation of US Periodic Adverse Drug Experience Reports (PADERs), forwarding ADEs to other manufacturers, and archiving ICSRs. Ms. Domin assists in the preparation of SOPs. For example, her signature is listed on SOP US-PV-022 v03, Regulatory Filing of Expedited Adverse Event Reports, as one of the preparers. See Exhibit 22, page 1. She stated that she works for Dr. Rullo and this is documented on the Organizational Chart for US Drug Safety. See Exhibit 15.

(b) (6) Senior Manager, Submissions, US Pharmacovigilance

Ms. (b) (6) answered questions related to the preparation of US PADERs. This included how she assembles lists of cases and contacts other departments such as US RAMP for information. She works in the Case Management group for Ms. Domin.

Don Klaproth Jr., Director, Local User Support (LUS) & Compliance

Mr. Klaproth provided information on the ADE training his group coordinates and performs for the firm and also the proactive compliance monitoring done by his group. He reports to Peter Thome, Senior Director, Local User Support (LUS) Quality Documents and Compliance, who in turn reports to Dr. Rullo.

(b) (6) Senior Manager, Regulatory Submissions, US Regulatory Affairs Marketed Products

Ms. (b) (6) answered questions on the firm's processes for preparing NDA Annual Reports, inclusion of clinical studies to NDA Annual Reports, and requesting information from other departments required for NDA Annual Reports. Her group's responsibilities include preparation of NDA Annual Reports. She participated in some daily wrap-up meetings and also in the closeout meeting at the conclusion of the inspection. Her signature appears on SOP US-EG-007 v02, NDA Annual Reports, as one of the preparers. See Exhibit 19, page 2. She reports to Craig M. Audet, Vice President, US Regulatory Affairs Marketed Products. The Organizational Chart for US Regulatory Affairs Marketed Products documents this. See Exhibit 12, page 2.

Barbara Rullo, MD, Vice President, Drug Safety, US Medical Affairs

Dr. Rullo stated that she is the most responsible person for US Pharmacovigilance. This department is comprised of a staff of (b) (4) including Medical Information Services. She said that physicians within her department are organized by therapeutic areas such as Internal Medicine, Oncology and Urology. She answered questions throughout the inspection on her department's processes and assisted in providing requested information. This included information related to 15-day late reports and compliance monitoring. She was present throughout the inspection and participated in all daily wrap-up meetings as well as the closeout meeting at the conclusion of the inspection.

Dr. Rullo said that she reports to Paul H. Chew, MD, US Chief Science Officer/Chief Medical Officer. This is indicated on the Organizational Chart for US Medical Affairs. See Exhibit 14, page 3. Her direct reports within Drug Safety (aka US Pharmacovigilance) include Rosalina Domin, Senior Director, Case Management, Peter Thome, Senior Director, Local User Support (LUS), Quality Documents & Compliance, Karen Simpson, MD, Senior Director, Resources and Projects, and Linda Scarazzini, Associate Vice President, US Risk Identification, Surveillance & Communication. Organizational Charts for Drug Safety are attached as Exhibits 14, page 4, and 15.

The roles and responsibilities of US Pharmacovigilance (aka Drug Safety) and the Affiliate Pharmacovigilance Head (i.e., Dr. Rullo) are outlined in SOP US-PV-012-v03, Organization, Roles and Responsibility of sanofi-aventis US Pharmacovigilance. See Exhibit 20. Dr. Rullo was the approver for this SOP and other department SOPs such as Regulatory Filing of Expedited Adverse Event Reports. See Exhibit 22.

Linda Scarazzini, MD, Associate Vice President, US Risk Identification, Surveillance & Communication (RISC), Drug Safety

Dr. Scarazzini attended some daily wrap-up meetings and the closeout meeting at the end of the inspection. She answered questions related to the medical assessment of cases and reasons for late 15-day reports. Her group reviewed lists of potentially late 15-day reports and indicated the reasons for lateness. Affiliate Safety Officers (ASOs) work in her group. ASO responsibilities include case review, medical review of serious ICSRs and assessing them for expectedness with the US label, and

some risk management. She reports directly to Dr. Rullo. See Drug Safety Organizational Chart attached as Exhibit 15.

Karen Simpson, MD, Senior Director, Resources and Projects, US Pharmacovigilance

Dr. Simpson stated that she is responsible for budget and administrative functions within the department. She said she also performs some signal detection activities. She was present throughout the inspection and along with Peter Thome, Senior Director, Local User Support, Quality Documents and Compliance, coordinated most of my requests for information and staff interviews. She attended each daily wrap-up meeting and the closeout meeting at the end of the inspection. She reports to Dr. Rullo. See Drug Safety Organizational Chart attached as Exhibit 15.

Peter Thome, Senior Director, Local User Support (LUS), Quality Documents and Compliance

Mr. Thome said that his group's responsibilities include coordinating the preparation of Standard Operating Procedures (SOPs) with Subject Matter Experts (SMEs), interfacing with business partners, developing local Safety Data Exchange Agreements (SDEAs), ADE training, metrics and proactive compliance monitoring, and Corrective and Preventive Actions (CAPAs). He was present for all but one day of the inspection and along with Dr. Simpson coordinated my requests for information and staff interviews. He attended daily wrap-up meetings and the closeout meeting at the conclusion of the inspection. He reports directly to Dr. Rullo. See Drug Safety Organizational Chart attached as Exhibit 15.

Katy Sotirov, Associate Vice President, Quality Systems and Support

Ms. Sotirov was present throughout the inspection and attended daily wrap-up meetings and the closeout meeting at the end of the inspection. She assisted Mr. Thome and Ms. Simpson with coordinating my requests for information. She provided information on the firm's Quality & Compliance function and clinical study databases. She said that she worked for Nora Poliakoff, Vice President, Quality [(b) (6)] who in turn reported to Gregory Irace, President & Chief Executive Officer (CEO). She said that previously she was Associate Vice President, Good Clinical Practice (GCP), US Quality & Compliance. She was listed as the reviewer for certain SOPs such as SOP UV-PV-009 V02, Pharmacovigilance Training for sanofi-aventis Employees, Contractors and Agents. See Exhibit 24. She said that her role within US Quality & Compliance had recently changed and that GCP and Pharmacovigilance responsibilities were being assumed by Research & Development (R & D). Her new responsibilities will include US Medical Affairs, Regulatory Affairs, Promotional Labeling and Grants.

Organizational Charts for US Quality & Compliance are attached as Exhibit 16. Organizational Charts for R&D Quality Operations are attached as Exhibit 17. The index of SOPs where there is local and global auditing responsibility over US Pharmacovigilance is attached as Exhibit 21.

Paul H. Chew, MD, US Chief Science Officer/Chief Medical Officer

Dr. Rullo said that she reports directly to Dr. Chew. His Medical Affairs responsibilities include US Regulatory Affairs Marketed Products (RAMP) and Drug Safety. Although Dr. Chew was not present throughout the inspection, he did introduce himself during the inspection and was present for the closeout meeting. Dr. Chew signed the contract with [redacted] (b) (4) See Exhibit 123, page 15. He also approved SOP No: US-PV-001 v04, Preparation of Periodic Reports and PSUR Waivers for Submission to the FDA. See Exhibit 54, page 2. As Chief Medical Officer, Dr. Chew is a member of the company's Recall Management Committee. See Exhibit 25, page 4.

Dr. Chew reports directly to Gregory Irace, President and CEO. The Organizational Chart for Pharmaceutical Operations, US Commercial Team, documents this. See Exhibit 14, page 2. Mr. Irace reports to Hanspeter Spek, President Global Operations, who in turn reports to Christopher Viehbacher, Chief Executive Officer, for sanofi-aventis. This reporting structure is documented in the US Organizational Chart (Exhibit 13, page 2) as well as the company's 2009 Annual Report. See Exhibit 2, page 10. Mr. Irace approved some company SOPs. For example, he signed SOPs for Pharmacovigilance Training for sanofi-aventis Employees, Contractors and Agents, Recall of A Marketed Product, and Drug Product Quality Complaint Processing (Exhibits 24, 25 and 128).

Other sanofi-aventis US LLC staff interviewed and/or providing requested information during the inspection included:

Lesley Fierro, M.S., PharmD, Associate Vice President, Medical Information Services, US Medical Affairs
Daniel Gil, MD, Senior Director, US Risk Identification, Surveillance & Communication (US RISC), Drug Safety
[redacted] (b) (6) MD, Affiliate Safety Officer, US Pharmacovigilance
James A. Parker, Jr., Associate Vice President, US Regulatory Affairs Marketed Products
[redacted] (b) (6) Analyst, Case Receipt & Retention, Case Management
[redacted] (b) (6) Senior Manager, Metabolics/Devices/Product Technical Complaints (PTCs), Case Management
[redacted] (b) (6), Analyst, Case Receipt & Retention
[redacted] (b) (6) Senior Manager, SDEA & Quality

In addition, the following staff from Global Pharmacovigilance & Epidemiology (GPE), the corporate pharmacovigilance department, also participated in the inspection:

Patricia Bocciarelli, Senior Manager Pharmacovigilance, GPE Quality & Compliance, sanofi-aventis Research & Development, Chilly Mazarin, Cedex-France

Ms. Bocciarelli discussed inspection findings from the June 2009 FDA inspection in Chilly Mazarin and follow-up actions the firm had taken.

Patrick Caubel, MD, Vice President, Global Pharmacovigilance and Epidemiology (GPE), Bridgewater, NJ

Dr. Caubel gave an (b) (6) Overview presentation during the inspection. This included background on the legacy systems, discussion of reporting compliance for 15-day reports, a summary of issues with the (b) (6) system, and system changes to maintain compliance. He said that he recently joined the GPE group in Bridgewater, NJ and that he was previously Vice President and Global Head, Pharmacovigilance and Medical Safety Analysis, Global Pharmacovigilance (PV), for sanofi pasteur in Swiftwater, PA. Dr. Caubel was present for the closeout meeting at the end of the inspection. GPE's Detailed Description of the Pharmacovigilance System (DPPS) includes information on the sanofi-aventis corporate PV organization and systems. A copy of version 3.0 of the DPPS dated February 4, 2010 is attached as Exhibit 18. An Organizational Chart for GPE was included in the DPPS, Exhibit 18, page 56.

Tsilla Elhadad, MD, Associate Vice President, GPE, Pharmacovigilance Regulatory and Coordination Unit (PRCU), Bridgewater, NJ

Dr. Elhadad was present for part of the inspection, several daily wrap-up meetings and the closeout meeting at the end of the inspection. She provided information on preparation of Periodic Safety Update Reports, handling of safety studies and Health Authority Commitments, and inspection findings from the June 2009 FDA inspection.

(b) (6) R.N. M.H.A., Assistant Director, Head of Global User Support, GPE, PRCU, Bridgewater, NJ

Mr. (b) (6) discussed the actions the firm had taken since (b) (4) roll out to address a clock date display issue with migrated cases.

Dan Sum, Deputy Head, System Support Unit (SSU), (b) (6) Validation Lead, and (b) (6) Project Manager Deputy/Information Systems (IS) Lead, GPE, Bridgewater, NJ

Mr. Sum, (b) (6) provided information related to the computer system validation of the (b) (4) AE Reporting System that was conducted by GPE.

FIRM'S TRAINING PROGRAM

A Standard Operating Procedure (SOP) was available for training of US Pharmacovigilance Staff. In addition, the firm has a SOP for PV training of sanofi-aventis employees, contractors, and agents. Copies of these SOPs are attached as Exhibit 23 and 24. Mr. Klaproth provided an overview of the firm's training programs for both PV staff and other employees that included an on-line training module. All company employees and contractors are trained so that they know to report ADEs. Each year all (b) (6) US employees receive this training and compliance metrics were available to show that at least 99% of the employees completed the training on-time. He said that there was also a training module on a CD that is used for contractors/vendors and outside counsel. Employees are instructed to report an ADE to an 800 number. However, there is also an Adverse Event Reporting Form on the company web that can be submitted electronically or faxed. A copy of this form is attached as Exhibit 26.

Training curricula have been established for PV employees. Training records, curriculum and resumes were requested for three PV employees and reviewed. All required training was completed and no issues were noted.

ADVERSE DRUG EXPERIENCE (ADE) REPORTING

The Drug Safety department, aka US Pharmacovigilance, at this firm is responsible for processing all domestic spontaneous ADEs received for US marketed products, preparation of US Periodic Adverse Drug Experience Reports (PADERs), and a small number of clinical study cases. Dr. Rullo said that they are starting to take responsibility for handling reports from US Medical Affairs clinical studies. She said that these Phase IV studies may or may not be under an IND. Ms. Domin said that up until last year around 99% of cases they processed were spontaneous. US Pharmacovigilance is responsible for determining the expectedness (i.e. listedness) against the US label for all ADEs reported to the FDA, whether from domestic or foreign sources.

Data entry and processing for all foreign case reports and the vast majority of clinical study cases, are the responsibility of the company's Global Pharmacovigilance & Epidemiology (GPE) department located in France and at another site in Bridgewater, NJ. Periodic Safety Update Reports (PSURs) are prepared by Global Safety Officers (GSO) within GPE. GPE sends cases to affiliates for reporting to their respective Health Authorities. GPE's Detailed Description of the Pharmacovigilance System (DPPS) provides an overview of the sanofi-aventis corporate PV organization and systems. A copy of version 3.0 of the DPPS dated February 4, 2010 is attached as Exhibit 18.

Generally, Aventis legacy products are handled by GPE in Bridgewater, NJ and Sanofi legacy products are handled in France. Data entry activities i (b) (4) for these therapeutic areas are done in Bridgewater, NJ: Oncology, Metabolism/Endocrine, Rheumatology, Anti-infective Respiratory, Devices and Dermatology (former Dermik products). Data entry activities for these products are done in Chilly Mazarin: Cardiovascular/Thrombosis, central Nervous System, Internal Medicine and Generics/OTCs. A product list was provided indicating what Global Pharmacovigilance &

Epidemiology (GPE) site is assigned to each product worldwide. It is attached as Exhibit 5. The GPE product assignment list for US marketed products was provided during the June 2009 inspection of sanofi-aventis in France. See Attachment 5.

There are 7 sanofi-aventis sites responsible for complete data entry, also referred to as Fully Connected Sites or FCS. There are two Corporate GPE sites that are located in Bridgewater, NJ and Chilly Mazarin, France. Other fully connected sites are located in Frankfurt, Germany, Paris, France, Bridgewater, NJ (the US affiliate), Milan, Italy, and Tokyo, Japan. Some local affiliates have limited data entry rights and are called key data entry sites or KDS. Other local affiliates have no (b) (4) access rights and are called Non Connected Sites or NCS.

All FDA submissions to the NDA are done by US Regulatory Affairs Marketed Products staff at this location. Some Serious Adverse Events (SAEs) from IND clinical studies are processed here. However, all submissions to the IND, including IND safety reports for clinical studies, are done by Global Regulatory Affairs personnel in Malvern, PA, not by this firm, the US affiliate.

On November 9, 2009, the firm started utilizing (b) (4) (b) (4) AE Reporting System (AERS) for data entry, coding, tracking and reporting individual case safety reports (ICSRs). Adverse events associated with medical devices the company markets are also entered in (b) (4) The firm's two legacy systems (b) (4) (b) (4) were not used after (b) (4) was released to production. Ms. Domin said that her group had previously utilized both versions of (b) (4)

Ms. Domin provided an overview of case processing (Exhibit 27). US cases are received via phone, fax, email, postal mail, and from literature review. They are then logged into (b) (4) a corporate database, also used for Medical Information and product quality complaints. Case data from (b) (4) is then reviewed and entered into (b) (4) There is no electronic transfer of data from (b) (4) into (b) (4) Generally only serious ADEs are reviewed by physicians, the Affiliate Safety Officers. The process for handling spontaneous ICSRs is described in SOP US-PV-002 v04, Handling Unsolicited Individual Case Safety Reports for Registered/Marketed Products in the United States. See Exhibit 29.

Most US cases received via phone are handled by their Medical Information call center, (b) (4) (b) (4) enters all cases into (b) (4) The current (b) (4) contract was reviewed and no issues were noted. Case Management reconciles ADEs in the (b) (4) database and (b) (4) on a daily basis.

(b) (4) (b) (4) is another Medical Information call center used by the firm. It is used for handling calls associated with Heritage products where there is a lower call volume. Heritage products are older products no longer promoted by the firm but still marketed. A list of Heritage products is attached as Exhibit 28. The (b) (4) SOP for Adverse Event Reporting was received and no deficiencies were

found (b) (4) enters ADEs into their own database, not into (b) (4) Snapshots of ADE information are forwarded to US Pharmacovigilance (USPV) at sanofi-aventis US LLC. USPV reconciles cases in the (b) (4) database against their database on a weekly basis.

OVER-THE-COUNTER ADVERSE EVENT (OTC AE) REPORTING

sanofi-aventis US LLC markets one OTC drug product without an NDA/ANDA. It is Zephiran Chloride (benzalkonium topical solution). See product listings attached as Exhibits 3 and 4. I requested a listing of ADEs received for this product since January 2008. The firm received one ADE on April 24, 2008 and it was not serious. No other ADEs were received. See Exhibit 32. See the General Discussion with Management section below, item no.7, regarding the company's SOPs for OTC AE reporting.

ADE WRITTEN PROCEDURES

An index of US Pharmacovigilance SOPs was requested. Mr. Thome said the US affiliate has their own quality documents or local SOPs that they follow. An index of these SOPs is attached as Exhibit 33. He said that his group does an assessment of all global quality documents to determine if their SOPs need to be changed or if there is a need to develop a local document. There are also Job Aids used in US Pharmacovigilance. See the General Discussion with Management section below, item, no. 7, regarding Job Aids.

15-DAY REPORTS

A listing of late 15-day reports submitted to the FDA from January 1, 2009 to present (end of March 31, 2010) was requested on the first day of the inspection. Dr. Rullo said that Global (aka GPE) would generate the report. Two lists of late cases were provided, one for the period of January to November 2009 ((b) (4) cases) and another for the period of November 2009 to March 2010 (b) (4) cases). These are for spontaneous cases. The listing of late submissions for cases entered in (b) (4) indicated that there were 195 late cases. See Exhibit 34. The listing of late submissions for cases entered in (b) (4) included 296 cases. See Exhibit 35. A presentation given by Dr. Caubel also stated that 296 spontaneous cases were reported late to the FDA since (b) (4) roll-out (November 9, 2009). See Exhibit 49, page 5.

I subsequently selected late cases from each of the late submission lists and reviewed the Medwatch forms and source documents. Many of the cases I reviewed were not truly late cases, especially with cases listed as late on the (b) (4) list. For example, there were sometimes two dates on the Medwatch form in block G4 (Date received by manufacturer). Ms. Domin said that (b) (4) included two dates in this block for follow-up cases: the first awareness date for initial receipt of information by the company and the awareness date for receipt of follow-up information. The reports provided showed late submissions based on the first awareness dates. In addition, the date in

block G4, did not always match the date of follow-up information noted in the narrative description in block B5 (Describe event or problem). Ms. Domin said that in (b) (4) the date had to be manually changed in block G4 to reflect the receipt date of follow-up information and if it wasn't, the case appears to be reported late when it is not. These are considered clock date issues. Dr. Rullo and Ms. Domin said that when their physicians are preparing aggregate reports (i.e., periodic safety reports), they review cases. At that time, a physician may interpret the case differently than the physician who initially reviewed the case and update the narrative section of the case. This information may or not be significant but it is resubmitted as a follow-up case. There were also submissions of duplicate or deleted cases that appeared to be late and late reports for Lantus where the report was related to the medical device portion of the product, not the drug itself.

The firm subsequently reviewed individual cases listed as late and provided revised listings on other inspection dates that included the reasons for lateness and filtered out cases that were not truly late. The dates of the listings are usually in the footers in the excel format spreadsheets. Cases that are not truly late included duplicate or deleted cases or cases where submission was not needed such as the follow-up report did not include significant information. Separate listings were provided for paper submissions and for Drug Device Combinations. Listings of late paper submissions had to be manually generated by the firm and included some clinical study cases. For Drug Device Combinations, Dr. Rullo said that the reporting timeframe is 30 days for medical devices. For example, Lantus Solostar (insulin glargine) injection is a combination medical device/drug product and subject to different reporting rules.

As I reviewed the Medwatch forms and source documents for cases on the updated late 15-day report submission lists, I found a few additional 15-day reports that were not truly late. Revised 15-day report late submissions lists are attached as Exhibits 36 to 47. The last listings provided on April 26, 2010 for late 15-day report submissions from January 1, 2009 through March 31, 2010 are attached as Exhibits 45 and 46. Based on the revised lists, the firm provided overall compliance data stating that there were 312 late 15-day reports from January 1, 2009 through March 31, 2010. See Exhibit 43. The initial reports provided indicated that there were 491 late cases during this period. It should be noted that this compliance data does not include paper submissions. In addition, it was not possible for me to confirm that all 15-day reports listed as late were actually late without reviewing every case and discussing it with the firm.

When Medwatch forms are printed out in (b) (4) the report date in Block B5 is the print date, not the actual date it was submitted, and the top of the form states it is a Draft. Ms. Domin said that this occurs with Medwatch forms printed out from (b) (4) The actual submission date shows in the (b) (4) submission printouts in the case files and in the system itself.

On May 7, 2010, the firm provided listings for their April 2010 15-day report submissions. There were 852 submissions with 24 of them being late. This was on-time compliance of 97.2%. See Exhibit 48.

Mr. Thome said that his group was responsible for Compliance Monitoring in US Pharmacovigilance. These activities are outlined in SOP No.: US-PV-031 v03, Compliance Monitoring in US Pharmacovigilance. See Exhibit 50. He said there were monitoring tools available with the (b) (4) system that enabled the company to proactively identify late cases. He said that his group did compliance monitoring for (b) (4) version while the global compliance function was responsible for (b) (4) He added that while the global compliance function did the monitoring that his group would follow-up if requested.

Both Mr. Klaproth and Mr. Thome said that proactive compliance monitoring was suspended as there were no available tools with the new safety database, (b) (4) Mr. Klaproth gave an overview of the compliance monitoring his group had done for (b) (4) In 2007, only 88.13% of submissions were on time. After proactive compliance monitoring was started and Corrective and Preventive Actions (CAPA) taken, on time submissions were 99.61% and 99.58% in 2008 and 2009 respectively until (b) (4) was put into production. See Exhibit 51, pages 2 and 3. It should be noted that these on time submissions involved cases under their control, not cases reported to them from GPE. For example, the root cause for around 60% of late FDA submissions in the first three quarters of 2009 was late distribution from GPE. See Exhibit 51, page 4. Some CAPAs were reviewed for late cases such as failure to update the case downgrade status. Copies of these CAPAs are attached as Exhibits 52 and 53.

Mr. Thome said that the global compliance function is in France and that the global organization was developing monitoring tools for (b) (4) He said that they are able to identify and follow-up on some late cases now but not to the extent they did when a monitoring tool was available.

Some Multaq and Oforta 15-day reports listed in PADERs were selected for review. For these and 15-day late reports reviewed, both Medwatch forms and other source documents were reviewed. Documentation was available to demonstrate follow-up by both telephone and/or mail to obtain additional information. Follow-up is only done here for local cases. The GPE group conducts follow-up activities for foreign cases.

Paper submissions were done for clinical study cases. Initially there were technical issues with Oforta and Multaq cases and all 15-day reports were also submitted via paper. These issues were resolved and electronic transmission is now done.

PERIODIC SAFETY REPORTS

Ms. Edom provided information on the preparation of US Periodic Adverse Drug Experience Reports (PADERs). This included how she assembles lists of cases and contacts other departments such as US Regulatory Affairs Marketed Products (RAMP) for information. SOP NO: US-PV-001v04, Preparation of Periodic Reports and PSUR Waivers for Submission to the FDA, is attached as Exhibit 54. Ms (b) (6) said that her group prepares a schedule each year for the PADERs and

PSURs that are required to be prepared and/or submitted. The schedule for 2010 is attached as Exhibit 55.

Periodic safety reports reviewed during this inspection included the PADERs for Apidra, Multaq and Oforta and Periodic Safety Update Reports (PSURs) for Ambien, Elitek, Eloxatin, and Ketek. PSURs are not prepared by the US Affiliate but by the company's two Global Pharmacovigilance & Epidemiology sites. However, they are submitted to the FDA as the company has waivers to submit PSURs in lieu of PADERs for many of their products. The GPE SOP for PSURs is attached as Exhibit 56.

I requested a listing of aggregate safety reports that had been submitted late from January 2008 to present. It is attached as Exhibit 57. Mr. Thome said that one PADER had been submitted late in 2008. It was the quarterly periodic report for NDA 21-909, Allegra Oral Disintegrating Tablets, submitted on February 25, 2008. It was due on February 25, 2008 and submitted electronically that day. He said it was considered late because of that. He said its submission was delayed because responsibility for this product was transferred from global to local regulatory affairs.

Mr. Thome said that Global Safety Officers within GPE perform most of the trending and signal detection activities. US Affiliate physicians participate in this process by reviewing monthly reports of ICSRs received in the US and when aggregate reports are prepared. This is covered by SOP US-PV-003 v02, Supporting GPE Signal Detection for Registered Products in US Pharmacovigilance. See Exhibit 58. Documentation for the most recent local signal detection review for Multaq and Oforta was requested. Completed US Aggregate Data Review Acknowledgement Forms were provided and indicated that no signal had been detected. See Exhibit 59.

See the General Discussion with Management section below, item no. 5, for inspection findings related to periodic safety reports.

AWARE AERS (AE REPORTING SYSTEM)

sanofi-aventis started utilizing [(b) (4)] AE Reporting System (AERS) for data entry, coding, tracking and reporting individual case safety reports (ICSRs) on November 9, 2009. AWARE is also used for adverse events associated with medical devices. Use of their two legacy pre-merger software systems, [(b) (4)] and [(b) (4)] was stopped when the [(b) (4)] system was released to production. However, GPE still has access to [(b) (4)]

A high level review of the documentation associated with the computer system validation (CSV) for [(b) (4)] was done during this inspection. The validation project is referred to as the [(b) (4)] It should be noted that the CSV for [(b) (4)] was

done by Global Pharmacovigilance & Epidemiology, not the US affiliate, sanofi-aventis US LLC. Some US affiliate staff participated in the User Acceptance Testing (UAT).

The Validation Summary Report for (b) (4) at the time it was released into production was requested. An Interim Validation Report (IVR) signed November 9, 2009 was provided and is attached as Exhibit 60. Mr. Sum said that the projected completion date for a final Validation Report was 180 days (from release). He said that the timelines included for completion were working days, not calendar days. There were 6 pages of deviations requiring resolution on pages 30 to 35 in the IVR. One deviation was that the Traceability Matrix did not include mapping to Functional Specification and System Elements with a target to be completed in 90 days. See Exhibit 60, page 33. Tracking documents showing the status of deviations that required resolution in the (b) (4) Validation Summary Report were requested and provided. See Exhibits 63 to 65. The Traceability Matrix was listed as an open item. See Exhibit 63, page 4. Ms. Veltman said that the Traceability Matrix had been completed and reviewed but was being checked again.

The (b) (4) Validation Plan listed the Traceability Matrix (TM) as one of the deliverables. It stated that a formal traceability matrix would be used to ensure that user requirements (Requirement Specifications) are met and traceable through specifications (Functional and Technical Specifications) to system and user acceptance testing. See Exhibit 61, page 15. A copy of the most recent version of the Traceability Matrix was requested and provided. It is Version 2 and is still a Working Copy, not signed as approved. See Exhibit 62. For many requirements, the TM stated that functionality was either not implemented or not available. Some 21 CFR Part 11 requirements were on pages 105 and 106 of the TM. User Requirement R11-3-1 was that the system generates accurate and readable copies of all records in electronic format throughout the retention period. The TM stated that this functionality was not implemented and an applicable unit or user acceptance ID was not listed, only N/A for not applicable. See Exhibit 62, page 111. I asked Mr. Sum about this and he said that this was an error. He said that the application had this functionality and that it was OTB (out of the box).

A User Acceptance Test Design approved in August 2008 was available for the (b) (4) Data Migration that included data migrated from (b) (4) systems into (b) (4) For example, four runs starting in July 2008 and ending in August 2009 were done to migrate the data and resolve anomalies.

The log for Change Controls was requested and reviewed. After reviewing the content of the Change Control requests, I asked to see two major change controls for (b) (4) numbers 23751 and 23048. Change Control request 23751 involved correction of migrated cases on product information. Change Control 23048 was an Emergency Change Control request to change encoding. No ACKs (no acknowledgements) were received from the FDA. ICSRs failed to be submitted to the FDA system due to unsupported characters included in the narrative field. This included a quotation mark. The Change Control states that the submission failure (E2B) should have been detected by

running a specific query ([redacted] (b) (4) which is supposed to be run daily. 184 cases were identified. See Exhibit 66.

A listing of the 184 cases that were identified as not being properly acknowledged was requested. They are attached as Exhibit 67. Dr. Rullo said that the problem was detected by global (i.e., GPE) on December 2, 2009. She said that the company contacted FDA about the issue and was ready to send paper submissions. She said that FDA told them not to do this but to resolve the technical issues. A copy of the Government Agency Contact Report for the call that Craig Audet, Vice President, US Regulatory Affairs Marketed Products, made to the FDA on December 3, 2009 was provided and is attached as Exhibit 68.

Dr. Rullo said that most of these cases were clinical study cases and that the company did not know how many were late. She said she thought that most of them were but that the company would only be able to determine that by looking at each case. She said that there were actually more than 184 cases as there were additional cases submitted after December 2 until the issue was resolved. On December 7 and 8, 2009, the cases were successfully resubmitted to FDA in batches. She said that these cases were not included on the late 15-day submission reports provided me.

Mr. Sum said that as part of their validation activities, they went through a testing process with FDA. He provided a series of email messages between the company and FDA as the E2B certification. See Exhibit 72.

Mr. Sum and Ms. Veltman provided an overview of the E2B submission failure and the actions the firm took to correct it. Ms. Veltman said that the submission failures did not happen with all cases. She said it only occurred with cases if there was a non ASCI character in the narrative and this was not allowed with [redacted] (b) (4) She said that this was not an issue with their [redacted] (b) (4) legacy system as non ASCI characters were extracted. She said that they now have a workaround process where the narrative is copied into a notebook and then copied back into the system.

As previously stated, Change Control Request no. 23048 states that these submission failures should have been detected by running the query "[redacted] (b) (4) " which is supposed to be run daily. See Exhibit 66, page 3. Mr. Sum and Ms. Veltman said that with [redacted] (b) (4) the checks that were done were for Neg ACK and Pos ACK. I asked to see the test scripts that were done during [redacted] (b) (4) validation related to E2B submission flow. User Acceptance Tests (UAT) were provided and are attached as Exhibit 69. They did not include test scripts for no acknowledgement (No ACK). They included testing a case with positive acknowledgement (Case #1, Exhibit 69 pages 6 to 11) and a case with negative acknowledgement (Case # 2, Exhibit 69, pages 12 to 15). However, there were no test results for the negative acknowledgement, Neg ACK. Instead a line was drawn through the test scripts with a handwritten note that it was Not Applicable, KC, 20-May-09. See Exhibit 69, pages 12 to 15. I asked why this testing was not done. Mr. Sum said that they were not able to test for Neg ACKs in the FDA test environment. I asked how this was documented. He provided a copy of a series of email messages within the company and with the FDA regarding this.

See Exhibit 70. He did not initially provide a revised test plan or memo to the validation file. He later prepared and provided a summary of the changes to the test plan. See Exhibit 71. For some of the executed test scripts, including the Pos ACK script, the tester did not initial and date every step in the script. Instead lines were drawn through them. See Exhibit 69, pages 6 to 11.

Dr. Rullo and Ms. Thome said that the firm now runs reports on a daily basis to identify cases for which E2B transmissions are not successful. These queries are for Negative Acknowledgements (Neg ACK), No Acknowledgement (No ACK), and No Message Delivery Notification (MDN). US Pharmacovigilance had already drafted a Work Instruction for Report Verification. It is attached as Exhibit 73. It was revised to reflect the practice of doing these queries on a daily basis and was approved and effective prior to the conclusion of the inspection. See Exhibit 74. Training materials were provided related to the staff training given for E2B acknowledgements. See Exhibit 75. They involved positive and negative Acknowledgements. Dr. Rullo said that this was not stressed in the training. The training focused on positive and negative acknowledgements as with (b) (4) it was important to check for Neg ACK. She said that one of the training handouts mentioned the queries for No ACK and No MDN but that this was missed. See Exhibit 75, page 5.

While reviewing files for 15-day reports, I noticed that the Medwatch forms for some follow-up reports were identified as being Initial Reports in block G7 (Type of Report) and that the manufacturer receipt date in block G4 was the date of initial receipt of information instead of the receipt of the follow-up information. Ms. Domin said that this was a clock date issue with (b) (4) and the data migrated from (b) (4) If a case was initially entered in (b) (4) and follow-up information for the case was received and entered after (b) (4) went live, the Medwatch form shows it as an initial report and first awareness date prints on the Medwatch form.

An example of a case with this clock date issue was Manufacturer Report (Case) No. 200915406US for Lantus. Initial information was June 17, 2009. See Exhibit 205, page 2. Additional information was received on October 28, 2009. It was not submitted to the FDA as a follow-up report until March 2, 2010. Block G of the Medwatch form states that this is the Initial 15-Day rather than a 15-Day follow-up. Also there is an inaccurate receipt date of June 17, 2009, the initial awareness date, not the awareness date for receipt of additional information. See Exhibit 205, pages 23 and 24.

The Medwatch form for case no.200915406US had a report date of April 26, 2010 in lieu of the actual submission date of March 2, 2010. As discussed in the 15-Day Reports section, when Medwatch forms are printed out in (b) (4) the report date in Block B5 is the print date, not the actual date it was submitted, and the top of the form states it is a Draft. Ms. Domin said that this occurs with Medwatch forms printed out from (b) (4) The actual submission date shows in the (b) (4) Submission printouts in the case files and in the system itself.

I asked the firm what steps have been taken to address the clock dates issue on Medwatch forms for migrated cases. Specifically, the initial receipt date, not the follow-up receipt date, is displayed on Medwatch forms if the report was initially entered in the (b) (4) system and the follow-up

information was received and entered in [(b) (4)] Mr. Murphy explained that this occurs when the first non-significant information for a migrated case from [(b) (4)] is entered in [(b) (4)] He said that the system does not detect that the case has been already submitted to the FDA and this results in a submission as a potentially reportable case. He said that PV staff were reminded to review potentially reportable cases to avoid submission of cases with non-significant changes. He said that they just received a patch from [(b) (4)], are doing regression testing and that this issue would be fixed by July 2010. He provided a summary of actions taken since [(b) (4)] roll-out to address the clock date display issue for migrated cases. See Exhibit 77.

Dr. Caubel provided an overview of the [(b) (4)] system that included discussion of issues since roll-out. Some system changes were done and more were planned to maintain compliance. See Exhibit 49. He said the firm had just contracted with the consulting firm [(b) (4)] to assist them in resolving issues.

See the General Discussion with Management section, item # 2, below for an overview of inspection findings related to [(b) (4)] system.

LITERATURE SEARCHES

Dr. Gill said that literature searches are done here products marketed only in the US. All other literature searches are done by GPE. He provided a listing of local products that they conduct literature searches for. He showed me examples of some recent literature searches. SOP No. US-PV-007 v03, Scientific Literature Screening for sanofi-aventis Products, covers this process. See Exhibit 79.

NDA ANNUAL REPORTS

The two most recent NDA Annual Reports submitted to FDA for Eloxatin, Multaq and Oforta were requested. A Multaq NDA Annual Report was not available as none had been prepared. The NDA approval date was July 1, 2009 and the report is not due until September 1, 2010. NDA Annual Reports for Oforta and Eloxatin were reviewed. Periodic Safety Reports were also reviewed to assess consistency in reporting of clinical studies.

Although the NDA for Oforta was approved on December 18, 2008, it was not marketed by the firm in the US until February 1, 2010. The sponsorship of both the IND and NDA was transferred from Antisoma to sanofi-aventis, US LLC on May 11, 2009. The firm receives ADEs for Oforta from Bayer Schering Pharma who manufactures for Antisoma. sanofi-aventis US submitted the first NDA Annual Report on February 16, 2010 and it was reviewed. No issues were noted.

NDA Annual Reports for Eloxatin (oxaliplatin injection), NDA 21-759, and Eloxatin (oxaliplatin for injection), NDA 21-492, were reviewed. NDA 21-492 was approved on August 9, 2002 and NDA 21-759 was approved on January 31, 2005. Although the firm stopped marketing oxaliplatin for injection after oxaliplatin injection was approved, the NDA for oxaliplatin for injection (NDA 21-492) is still active. The NDA Annual Report for Eloxatin (oxaliplatin injection), NDA 21-759, period of January 31, 2009 - January 31, 2010, was submitted on March 30, 2010. The cover letter stated that this annual report did not include studies that are only required to be submitted in accordance with 21 CFR 312.33, IND annual reports. In reviewing this NDA Annual Report, I noted that it included Clinical Study Reports dating back to at least 2002 as completed unpublished clinical trials. See Exhibit 80, page 4 to 8. I subsequently requested selected sections of the articles and clinical study reports included as completed unpublished clinical trials in this report. They are attached as Exhibits 81 to 112. Most were foreign studies.

I asked why these older clinical studies were now being submitted. Dr. Rullo said that after another pharmaceutical company received a FDA warning letter for not including all clinical studies in NDA Annual Reports that they started including them. I asked if anyone at the company checked with FDA as whether these studies should be included in the current reports or if they should amend previously submitted reports. She said they did not. She said that if there had been any significant issues that this would have been included in the NDA Annual Reports. She added that they would also contact FDA for a label change, if warranted.

Mr. Audet and Ms. (b) (6) said that US RAMP utilizes the company's two clinical study databases in preparing NDA Annual Reports. The company has two clinical study databases, (b) (4) was used starting in June 2002 and was an Aventis database. It is the database used for clinical studies sponsored by Research & Development (R & D). However, Medical Affairs studies may be in (b) (4) as standardization for the use of these two databases started in 2006. (b) (4) was a Sanofi database. It is managed by Global Medical Affairs and is used worldwide by the company's affiliates. Ms. Sotirov said (b) (4) included local studies that may or may not be IND studies. She added the term local study refers to who is funding the study, not where the study is conducted at. Mr. Audet said that sanofi-aventis management mandated the use of (b) (4) to affiliates in 2008.

Listings of studies in both the (b) (4) databases were requested and provided for products where NDA Annual Reports were reviewed. Mr. Thome said that all studies on the (b) (4) list were actually initiated, not just planned, even if no study dates were listed. Neither database routinely includes business partner studies. Mr. Thome said that a business partner study may be in the database if it is a joint study. Investigator Sponsored Trials (ISTs) can be either in the (b) (4) databases. To determine if the study was an IST, the firm contacted Medical Affairs as they maintain IST lists.

I asked what the firm's criteria were for including clinical studies in NDA Annual Reports. A copy of the draft US Medical Affairs Work Instruction, Quality Document ID: USMA-CLIN-RPT-WIN-

0003 was provided. It is attached as Exhibit 114. It stated that the following studies are to be included for both NDA Annual Reports and PADERs: Company sponsored clinical trials (Phase I-IV), Preclinical Studies, Registries (product only), Health Outcomes Studies, and EPI studies (GPE). Mr. Thome said that their criteria did not include Disease Registries, business partner studies or Investigator Sponsored Trials (ISTs).

Mr. Audet and Ms. (b) (6) said that if a clinical study is ongoing that it was included in the Other Postmarketing Studies section of the NDA Annual Report. If the study has been completed, it was reported in the completed Unpublished Clinical Trials section. They said that the firm had changed their criteria for listing clinical studies as completed Unpublished Clinical Trials. Previously a study that had the status of Last Patient Out (LPO), Last Patient Last Visit (LPLV), Database Lock (DBL) or Clinical Study Report (CSR) approved was reported as completed. Now the Clinical Study Report has to be submitted, not just approved before they report the study as Completed.

Mr. Audet said that after seeing the FDA warning letter the company took the most conservative approach. Previously he said that their understanding was that only safety studies/postmarketing safety commitments had to be reported and this was safety studies required by FDA. He said they wanted to be transparent so they started reporting every study in every country for all products whether it was 1 year or 10 years old. Ms (b) (6) said that the company had not gone back and done an overall assessment of what had not been reported. Instead, at time that an NDA Annual Report was due they reported what was in each of their two clinical study databases.

Mr. Audet said that it was also his understanding that clinical studies reported to the IND did not have to be reported again in the NDA Annual Report. He said that the cover letters for the NDA Annual Reports state that the annual report does not include studies that are only required to be submitted in accordance with the IND. See Exhibit 80, page 1, as an example. I asked if there had been any guidance, communication or documentation from FDA regarding this. I was told that the IND studies were included by reference in sanofi-aventis NDA Annual Reports. Their typed response attached as Exhibit 113.

Ms. (b) (6) said that the company starting including studies from the (b) (4) database to NDA Annual Report in April 2008. This is indicated on page 11 of SOP US-REG-006 v02, NDA Annual Reports. See Exhibit 19, page 12. Then in December 2009, they started including clinical studies from the R& D (b) (4) database in NDA Annual Reports. This was initiated as a result of discussions with the FDA Investigator during his June 2009 inspection of their firm in France. However, this is not reflected in the current SOP for NDA Annual Reports. Ms. (b) (6) said that this SOP is being revised.

The Eloxatin NDA Annual Report, NDA 21-759, period January 31, 2009 – January 30, 2010, included some study reports for US studies (Exhibit 80). They were (b) (4) (Exhibit 97) and (b) (4) (Exhibit 104). Study (b) (4) was an IND study and included in IND Annual

Reports. Study (b) (4) was a Phase IV study done from February 08, 2005 to July 24, 2007. Study (b) (4) is also referred to as the (b) (4) study. It was a prospective multicenter comparison of an (b) (4). The study synopsis is attached as Exhibit 104. There were other US studies reported as completed unpublished clinical trials in this NDA Annual Report that were done before either NDA 21-492 or NDA 21-759 were approved. They were (b) (4) (Exhibit 80, page 10). The following US studies were included on the (b) (4) list: (b) (4) (b) (4) The IND number was not included as was done for more recent IND studies. See Exhibit 173, pages 1 and 2.

Since late reporting of Eloxatin clinical studies was observed in NDA Annual Reports, additional NDA Annual Reports and Periodic Safety Reports for other products were selected for review. They were Ambien (NDA 19-908), Apidra (NDA 21-629), Elitek (BLA 103946) and Ketek (NDA 21-144). Generally only the last two or three Annual Reports were reviewed.

Dr. Rullo said that based on due dates for NDA Annual Reports that all retrospective reporting of clinical studies should be completed by December 2010. She said that these studies may or may not have been included in the IND. However, she said that if there were any Serious Adverse Events (SAEs) in these studies that PV would have entered them into their databases and submitted them to Health Authorities, as required. Mr. Audet said that Medical Affairs physicians have reviewed the clinical study reports from the older studies not previously submitted and that there have been no new safety issues.

Prior to the closeout meeting, Mr. Audet and Ms. (b) (6) provided copies of the Clinical Trial Decision Process for 2010 and draft updated Quality Documents for the NDA Annual Report Process. The Clinical Trial Decision Process 2010 outlines the process for retrospective reporting of clinical studies. See Exhibit 209. In addition to referencing the use of both the (b) (4) and (b) (4) databases, the Quality Documents require a review by US Medical Affairs to ensure the accuracy and completeness of clinical study data. See Exhibits 208 and 210 to 212.

Specific inspection findings related to clinical studies not reported or reported late to NDA Annual Reports are discussed in the Objectionable Conditions and Management's Response section, Observations #1 and 2, and General Discussion with Management, item no. 4 below.

WAIVERS

sanofi-aventis US LLC submits Periodic Safety Update Reports (PSURs) in lieu of US Periodic Adverse Drug Experience Reports (PADERs) for many of their products. Products for which they submit PSURs are noted on the US Periodic Report and PSUR Waiver Report for 2010. See Exhibit 55. Documentation of the waivers for PSURs for Arava, Elitek and Eloxatin was requested and

provided. See Exhibit 115. Documentation for waivers not to submit Medwatch forms for non-serious cases were also requested. They were provided and attached as Exhibit 116.

NON-COMMERCIAL DISTRIBUTION

This firm has non-commercial distribution programs. These include patience assistance programs, marketing programs, and prescription drug samples. Contracts are handled by Medical Information, not by US Pharmacovigilance. One of the vendors is the [redacted (b) (4)]. Mr. Thome said his staff provides training or training materials to these vendors. Mr. Klaproth provided an overview of ADE awareness training. He said that his group has a CD for the ADE training that is sent to vendors for their use.

SAFETY AGREEMENTS AND CONTRACTS

Mr. Thome said that his group is responsible for local agreements and that global Safety Data Exchange Agreements (SDEAs) are handled by GPE. He said that generally, but not always, the US affiliate handles local SDEAs if licensing is only in the US for a US partner. He provided a list of Local and Global Business Partners for US marketed products. See Exhibit 117. I asked if SDEAs were in place for all local Business Partners. He said they were not. An updated listing was provided indicating the status of local SDEAs. See Exhibit 118. Another listing was provided showing which company reports to FDA. See Exhibit 119. Copies of the local agreements for Oforta, Clomid, and Diabeta were requested and provided. See Exhibit 120. The agreement for Oforta is a Pharmacovigilance Agreement with Bayer Schering Pharma AG and Xanthus. Xanthus is the previous name used by Antisoma and Bayer Schering Pharma AG manufactures Oforta for Antisoma. The agreements with [redacted (b) (4)] were in draft. Mr. Thome said that they prioritize their SDEAs based on risk and sales volume. I asked if responsibilities for reporting of ADEs were included in the supply or other agreements with [redacted (b) (4)] and [redacted (b) (4)]. He provided a pertinent section of a contract that one of their predecessor companies (Hoechst Marion Roussell Inc.) had with the [redacted (b) (4)] a predecessor of [redacted (b) (4)] relating to Clomid (clomiphene citrate). It states that ADE reports shall be promptly submitted. See Exhibit 121, page 2. For Diabeta (glyburide), there were several agreements between Hoechst Marion Roussel (HMRI) and [redacted (b) (4)], a predecessor of [redacted (b) (4)], relating to glyburide. It states that [redacted (b) (4)] will promptly submit ADE information to HMRI. However, the Quality Agreement between [redacted (b) (4)] and sanofi-aventis US LLC that was signed in October 2009 states that all ADEs will be forwarded to sanofi-aventis within 1 business day. Mr. Thome said that the company has had business relationships with both of these companies for many years and that they have not had any issues with delays in reporting ADEs. He said that their goal is to receive ADEs within 3 calendar days from business partners. The firm does reconciliation of ADE data with their business partners. This process is addressed in SDEAs. An example of a SDEA where reconciliation of safety information is discussed is their agreement with UCB Inc. for Xyzal. See Exhibit 122, page 8.

POSTMARKETING COMMITMENTS

Dr. Elhadad from GPE discussed the firm's handling of post approval commitments. She also provided a written response outlining the firm's processes (Exhibit 124). The firm has two quality documents related to the tracking of post approval commitments. They are Corporate Regulatory Affairs Policy WW-CRA-GCRA-POL-0083, Post-Authorization Commitments/Post-Marketing Studies and Commitments, and GPE QSOP-001127, Risk Management Plan: General Process for New Product and LCM Conducted by International Development. The Risk Management Plan SOP describes the Watch group responsible for monitoring the effectiveness and status of commitments.

Mr. Audet said that US Regulatory Affairs Marketed Products does not have access to the global Health Authority commitment database. For FDA commitments, they utilize (b) (4) ormat spreadsheets for tracking of commitments. They along with related information are attached as Exhibit 124, pages 31 to 96. He said that when information on global Health Authority commitments (outside the US) is needed such as for NDA Annual Reports and PADERs, they obtain it from global. Examples of contacts made via email to global for their information and their response were provided when requested. The firm has non study post approval commitments as well. They include reporting all serious hepatic ADEs for Ketek and Arava as 15-day expedited reports. Case Management has special questionnaires that are completed. These are noted on the US Pharmacovigilance Adverse Event Routing Slip to remind staff that they must be completed. See Exhibit 125.

For the NDA Annual Reports and Periodic Safety Reports I reviewed, I did not observe any instances where postmarketing commitments were not addressed. However, one Elitek postmarketing commitment was not listed in the spreadsheets. See the General Discussion with Management, item no. 6, below.

I asked the firm is there were any Risk Evaluation and Mitigation Strategies (REMS) for their products. Dr. Rullo and Mr. Thome said that the only one was for Multaq (dronedarone). A copy of the REMS for Multaq is attached as Exhibit 126.

SANOFI-AVENTIS INSPECTION IN FRANCE

Inspectional findings from the June 2009 FDA PADE inspection of the firm's Global Pharmacovigilance & Epidemiology site in Chilly Mazarin, France that were relevant to the US affiliate were covered during this inspection. A FDA 483 was not issued. Dr. Rullo said that the company had not received a copy of the inspection report. In addition, they were discussed with Patricia Bocciarelli, Senior Manager, Pharmacovigilance, GPE Quality and Compliance, France and Tsilla Elhadad, M.D., Associate Vice President, GPE, Bridgewater, NJ.

One inspection finding was that GPE determined causality for spontaneous reports. Dr. Elhadad said that causality assessment was only used for signal detection and not for reporting to a Health Authority. She said that when they do signal detection that they consider all cases and trends and may look at causal relationships.

There was deletion of the original MEDRA classification when defined by the original reporter. Ms. Bocciarelli said that the case report involved lack of efficacy and that the product was not given for a label indication. Dr. Elhadad said that all information is recorded in their database and that the company may add their interpretation or assessment.

Another issue related to the training of US and Early Regulatory Assessment staff for specific FDA seriousness criteria to include "life threatening" and "hospitalization". Ms. Bocciarelli said that triage staff received training for seriousness criteria. She said that a business partner changed a case to serious but that their GSO (Global Safety Officer) said it was non-serious. Training records were reviewed during this inspection and staff here are trained in FDA seriousness criteria.

A business partner clinical study was in (b) (4) without additional information. Ms. Bocciarelli said that business partner studies are usually not tracked and normally not in their study database. She said she did not know why this study was entered in (b) (4)

Regarding lot triggers for potential manufacturing concerns, Ms. Bocciarelli said that the company does follow-up for trending and that a guide for this was provided to the CSO.

Another inspection finding was that there was unlimited access for nonclinical personnel in (b) (4). Dr. Elhadad said that this is no longer an issue since the firm no longer uses (b) (4) She explained that there was either browse access or write access. Write access was provided to staff registering cases. Now there are different levels of write access.

There was discussion regarding communication channels between Global Medical Affairs, International Clinical Development and Literature Reviewers especially as it may relate to US Periodic Reports and NDA Annual Reports. Ms. Bocciarelli said that previously there were two teams. Now there is one team within the organization.

A product complaint involving a mix-up with Lantus and distilled water was originally closed due to an unknown lot number. Ms. Bocciarelli said that she did not recall all the details but that the complaint originated in Germany. She subsequently provided me available documentation for PTC (Product Technical Complaint) # 1000367172. It was closed on June 12, 2009 without investigation as there was no batch number provided and no samples were available. See Exhibit 127.

Another inspection finding related to training templates for job descriptions and assessments of historical staff. Ms. Bocciarelli said that these are now kept at firm for staff who leave the company.

An issue was noted regarding the definition of "time zero". Ms. Bocciarelli said that time zero is when the 4 required elements are met. This was documented in procedural documents used by US Pharmacovigilance staff.

The delegation of pharmacovigilance responsibilities to contractors without performing a due diligence assessment of the contractor was discussed. Ms. Bocciarelli said that they audit their business partners and prepare questionnaires for them to complete on their PV systems. She said that they had audited (b) (4) She said that it is the responsibility of the affiliate to ensure audits are done. Ms. Sotirov said that the company does audit their contractors/vendors.

The inspection report also noted that the firm did not appear to provide FDA with studies in the Periodic Reports that are provided in NDA Annual Reports or Investigational New Drug reports. Refer to the NDA Annual Reports and General Discussion with Management sections of this report for related inspection findings.

COMPLAINTS

Product Technical Complaints (PTC) is handled by the US Product Quality Complaint group at this firm, the US affiliate. Complaints are documented in the Global Product Technical Complaints (PTC) database. The same call center is used for product quality complaints as for ADEs. SOP No. US-QA-020 v05, Drug Product Quality Complaint Processing, covers product technical/medical complaints as well as product technical complaints and includes processes for US Pharmacovigilance staff to follow. This includes monthly reconciliation of complaints in their respective databases. See Exhibit 128.

RECALL PROCEDURES

The firm's procedures for recalls was requested and reviewed. No deficiencies were noted. The Recall Management Committee includes the Chief Medical Officer, US Medical Affairs. This is Dr. Chew. A copy of this SOP is attached as Exhibit 25.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

On May 13, 2010, a closeout meeting was held and a Form 483 (Inspectional Observations) was issued to Paul H. Chew, MD, US Chief Science Officer/Chief Medical Officer. Others in attendance were:

Craig Audet, Vice President, US Regulatory Affairs Marketed Products

Patrick Caubel, MD, Vice President, Global Pharmacovigilance & Epidemiology
Rosalina Domin, Senior Director, Case Management, US Pharmacovigilance
Tsilla Elhadad, MD, Associate Vice President, Global Pharmacovigilance & Epidemiology, PRCU
(b) (6) Senior Manager, Regulatory Submissions, US Regulatory Affairs Marketed Products
Linda Scarazzini, MD, Associate Vice President, US RISC, Drug Safety
Barbara Rullo, MD, Vice President, Drug Safety
Karen Simpson, MD, Senior Director, Resources and Projects, US Pharmacovigilance
Katy Sotirov, Associate Vice President, Quality Systems and Support
Peter Thome, Senior Director, Local User Support, Quality & Compliance

Observations listed on form FDA 483

OBSERVATION 1

An annual report did not include a status report for all post marketing studies being performed by, or on behalf of, the applicant and not covered by the requirements of 21 CFR 314.81(b)(2)(vii).

Specifically, Annual Reports were not complete as postmarketing studies were not reported or were submitted late.

1) Apidra (insulin glulisine injection) study APIDR_L_02012 was not submitted to any Annual Report for Apidra (NDA 21-629).

2) Elitek (rasburicase) studies RASBU_L_00351 and RASBU_L_01489 were not submitted to any Annual Report for Elitek (BLA-103946).

3) Eloxatin (oxaliplatin) studies OXALI_L_00737 and OXALI_L_00869 were not submitted to any NDA Annual Report for Eloxatin (oxaliplatin injection), NDA 21-759, or Eloxatin (oxaliplatin for injection), NDA 21-492.

4) Ketek (telithromycin) study TELIT_L_05072 was not submitted to any NDA Annual Report for Ketek, NDA 21-144.

5) Starting around April 2008, retrospective reporting was initiated to include clinical trials not previously reported to NDA Annual Reports as safety studies or postmarketing study commitments and/or to the IND. Some examples of clinical trials reported late are:

Ambien (zolpidem tartrate), NDA 19-908

Studies ALI5057, ALI5837, BEQ5835, BEQ5836, EFC6820, LTE5407, PDY6567, and PKD5070 were included in the NDA Annual Report for the period of December 16, 2008 - December 15, 2009 but not for the periods of December 16, 2006 - December 15, 2007 or December 16, 2007 - December 15, 2008.

Apidra (insulin glulisine injection), NDA 21-629

Studies APIDR_L_00348, APIDR_L_00449, APIDR_L_00968, APIDR_L_01556, APIDR_L_01913, APIDR_L_01963, APIDR_L_01978, APIDR_L_02044, APIDR_L_ 02083, APIDR_L_03024, HMR1964A/3506, HMR1964A/3516, HMR1964A/3516, and HMR1964A/4002, were included in the NDA Annual Report for the period of April 16, 2008 - April 15, 2009 but not for the period of April 16, 2007 - April 15, 2008.

Eloxatin (oxaliplatin injection), NDA 21-759, and Eloxatin (oxaliplatin for injection), NDA 21-492

Study PM_L_0239, an IND study, was initiated in March 2006. It was not included in the NDA Annual Reports for NDA 21-492, for the period of August 9, 2006 - August 8, 2007, or for NDA 21-759, for the periods of January 31, 2006 - January 30, 2007 or January 31, 2007 - January 30, 2008. This study was submitted in the NDA Annual Reports, NDA 21-492, for the periods of August 9, 2007 - August 8, 2008 and August 9, 2008 - August 8, 2009 as an ongoing postmarketing study. It was also listed as a completed unpublished clinical trial in the NDA Annual Report, NDA 21-492, for the period of August 9, 2007 - August 8, 2008. It was submitted again in the NDA Annual Report, NDA 21-759, for the period of January 31, 2009 - January 30, 2010 as an ongoing postmarketing study.

Studies EFC-7127, L_9570, OXALI_L_01376, OXALI_L_ 03917, and PML_0098 were not listed in either the NDA Annual Reports for NDA 21-492, for the period of August 9, 2006 - August 8, 2007, or NDA 21-759, periods of January 31, 2006 - January 30, 2007 and January 31, 2007 - January 30, 2008. Instead they were submitted to the NDA Annual Reports, NDA 21-492, for the period of August 9, 2007 - August 8, 2008, and/or NDA 21-759, for the period of January 31, 2008 - January 30, 2009.

Reference: 21 CFR 314.81(b)(2)(viii)

Supporting Evidence and Relevance:

As discussed in the NDA Annual Reports section of this report, NDA Annual Reports were reviewed for the last two or three reporting periods. Additional Eloxatin NDA Annual Reports were reviewed. The clinical study data in NDA Annual Reports was compared with the listings of clinical studies in the [redacted (b) (4)] databases. Key study dates such as First Patient First Visit and Last Patient Last Visit were frequently missing from the [redacted (b) (4)] study listings. Since study dates were not immediately available, the NDA Annual Reports were not checked for inclusion of these clinical trials. Clinical studies included on clinicaltrials.gov were also compared with those in NDA Annual Reports. IND Annual Reports for the last three reporting periods were requested and reviewed for Ambien, Apidra, Eloxatin, and Ketek and compared with clinical studies listed in NDA Annual Reports. See Exhibit 129.

Examples of ongoing studies not reported or reported late to NDA Annual Reports were listed on the FDA 483 and/or in this report. They are not all inclusive for the periods reviewed. Company sponsored Disease Registry studies and Investigator Sponsored Trials were on the study lists. The firm does not consider these studies reportable to NDA Annual Reports so they were not listed on the FDA 483 and/or discussed in this report. In addition, there may be older clinical studies that were not reported or reported late in NDA Annual Reports for the required periods. However, since most

of the NDA Annual Reports reviewed for the last 2 or 3 reporting periods, this was not assessed for prior reporting periods and documented.

Ambien

NDA Annual Reports for Ambien (zolpidem tartrate) CIV tablets, NDA 19-908, were reviewed for the periods of December 16, 2006 – December 15, 2007, December 16, 2007 – December 15, 2008, and December 16, 2008 – December 15, 2009. There were no clinical studies included in the NDA Annual Report, period of December 16, 2006 – December 15, 2007, as either ongoing other postmarketing studies or completed unpublished clinical trials. See Exhibit 141, pages 5 and 7. One study (ZOLPI_L_00150) was listed in the NDA Annual Report, period of December 16, 2007 – December 15, 2008, as a completed unpublished study. There were no ongoing postmarketing studies listed. See Exhibit 142, pages 3 and 4. However, in the most recently submitted NDA Annual Report, period of December 16, 2008 – December 15, 2009 (Exhibit 143), there were listings of completed unpublished studies where the Last Patient Last Visit (LPLV) date was in 1999 in addition to ongoing postmarketing studies. See Exhibit 143, pages 3 and 4. Mr. Audet stated that the most recent NDA Annual Report submitted showed studies included from the [redacted] (b) (4) database after the process changed in December 2009 to include them in addition to [redacted] (b) (4) studies.

Study listings from [redacted] (b) (4) were requested and reviewed. See Exhibits 144 and 145. A revised ClubNet study listing was provided that showed the full study title, primary objectives and the Report/Planned and Actual dates. It is attached as Exhibit 146. A third [redacted] (b) (4) listing was provided showing all studies. See Exhibit 147. The previous [redacted] (b) (4) listings had a filter applied to them so that only solicited studies were listed. A revised [redacted] (b) (4) list was also provided that showed the First Patient First Visit (FPLV) and LPLV dates for the studies. See Exhibit 148.

Studies ALI5057, ALI5837, BEQ5835, BEQ5836, EFC6820, LTE5407, PDY6567, and PKD5070 were included in the NDA Annual Report for the period of December 16, 2008 - December 15, 2009 as ongoing postmarketing studies. See Exhibit 143, page 4. However, they were not listed as either ongoing postmarketing studies or completed unpublished clinical trials in the NDA Annual Reports of December 16, 2006 - December 15, 2007 or December 16, 2007 - December 15, 2008. See Exhibits 141 and 142. These 8 studies were included on the [redacted] (b) (4) (R & D) listing with the study status of CSR (Clinical Study Report) Approval or Database Lock. They are older studies dating back to 2003. It is not know whether Clinical Study Reports were written for studies with a status of Database Lock as the [redacted] (b) (4) database was not always updated. See Exhibit 148, page 2.

It should be noted that study EFC6820 was an IND study. It was included in the IND Annual Report, period of July 16, 2006 – July 15, 2007. See Exhibit 149, pages 1 and 7-9. Study PDY6567 was not an IND study. However, it was included in IND Annual Reports for the periods of July 16, 2006 – July 15, 2007 and July 16, 2007 – July 15, 2008 as a completed study. See Exhibits 149,

pages 1, 7, 10 and 11 and 150, pages 1 and 9. The IND Annual Report, period July 16, 2008 – July 15, 2009, did not include any study information. See Exhibit 151, pages 1 and 5.

Apidra

NDA Annual Reports for Apidra (insulin glulisine injection), NDA 21-629, were reviewed for the periods of April 16, 2007 - April 15, 2008 and April 16, 2008 – April 15, 2009 (Exhibits 131, 132, and 135). The Apidra NDA Annual Report for the period of April 16, 2007 – April 15, 2008 only included unpublished clinical trials (completed studies) and not ongoing other postmarketing studies. The NDA Annual Report for the period of April 16, 2008 – April 15, 2009 included listings of both completed and ongoing clinical studies. See Exhibits 131, 132 and 135.

Study listings from (b) (4) were requested and reviewed against studies in the NDA Annual Reports. See Exhibit 133. A revised (b) (4) list was subsequently provided after I noticed that there were studies included in the NDA Annual Reports that were not included on the study listings. A filter to include only solicited studies was incorrectly applied to the first report. The revised (b) (4) study listing that includes both solicited and unsolicited studies is attached as Exhibit 130.

Study APIDR_L_02012 was listed on the revised (b) (4) study listing. It was a retrospective product registry study done in Sweden. The First Patient In (FPI) was February 25, 2007 and the Last Patient Last Visit (LPLV) was April 16, 2009. The Report/Planned date for this study is December 12, 2010. See Exhibit 130, page 4. The Study Outline Template for this study is attached as Exhibit 134, pages 11 to 14. This study had not been reported as it was not included in NDA Annual Reports for both the periods of April 16, 2007 - April 15, 2008 and April 16, 2008 – April 15, 2009. See Exhibits 131 and 132.

Based on study initiation dates in the clinical study listings, studies APIDR_L_00348, APIDR_L_00449, APIDR_L_00968, APIDR_L_01556, APIDR_L_01913, APIDR_L_01963, APIDR_L_01978, APIDR_L_02044, APIDR_L_ 02083, and APIDR_L_03024, HMR1964A/3506, HMR1964A/3516, and HMR1964A/4002, were ongoing during the period of April 16, 2007 – April 15, 2008. These studies are on one or both the (b) (4) listings. See Exhibits 130 and 133, page 2. They were included in the NDA Annual Report for the period of April 16, 2008 - April 15, 2009 but not for the period of April 16, 2007 - April 15, 2008. See Exhibits 131 and 132. Therefore, they were reported late.

Study (b) (4) was an IND study and had been included in the IND Annual Report for the time period of June 2, 2007 to June 1, 2008. Many of the studies reported late were non-interventional studies such as registry studies. However, others such as (b) (4) a multicenter study, were not. See Exhibit 130, page 7, for the primary objectives of this study. APIDR_L_02083 was reported to the PADER, period of January 16, 2008 – April 15, 2008 as initiated during the reporting period. See Exhibit 136, page 2. Other PADERs submitted starting in

February 2008 are attached as Exhibits 137 to 140.

Elitek

Annual Reports for Elitek (rasburicase), BLA-103946, were submitted in accordance with 21 CFR 314.81 (b)(2). See Exhibits 152, page 1 and 153, page 1. I asked Mr. Audet if the responsibility for this product was transferred from CBER to CDER. He said it was and provided a copy of a FDA April 9, 2004 letter stating this. See Exhibit 154. The firm also submits Annual Progress Reports for Postmarketing Commitments as required for BLAs. BB INDs for Elitek were not reviewed.

Annual Reports for Elitek, periods of July 12, 2007 – July 11, 2008 and July 12, 2008 – July 11, 2009 were reviewed. The only clinical studies included in these Annual Reports were for Postmarketing Study Commitments. See Exhibits 152 and 153. Ms. (b) (6) said that there is no index or section stating that there are no Clinical Study Reports in the Annual Report, period of July 12, 2008 to July 11, 2009 as with the previous Annual Report due to eCTD formatting. A screen shot of the files associated with the submission and a table listing available sections for reports was provided to document this. See Exhibits 155 and 156.

Study listings from (b) (4) were requested and reviewed against studies included in the Annual Reports. See Exhibits 156 and 158. An updated (b) (4) list with study dates was provided. See Exhibit 159. A revised (b) (4) list including all studies, not just solicited studies, was provided. See Exhibits 160 and 161.

Elitek studies RASBU_L_00351 and RASBU_L_01489 were included in the (b) (4) listing. See Exhibit 161, page 1. The FPFV date for study RASBU_L_00351 was October 17, 2007 and it is ongoing. The FPFV date for Study RASBU_L_01489 was July 1, 2007 and the LPLV date was June 15, 2008. Since clinical study reports were not available, the Medical Affairs Extended Synopsis Templates were provided for these studies. They are attached as Exhibits 164 and 165. Neither of these studies was submitted to the Annual Reports for Elitek reviewed. Therefore, they were not reported to Annual Reports.

The Elitek Periodic Safety Update Report (PSUR), time period of September 1, 2007 to February 29, 2008 lists three safety related studies as ongoing during the reference period: EFC4978, L-8905 and L_8392. See Exhibit 162. This PSUR was included in the submission on April 25, 2008. See Exhibit 163. Study EFC4978 was a postmarketing study commitment and listed in the Annual Reports as such. Study L_8392 was included on the (b) (4) list with a study status of first subject first visit of May 25, 2005 and no additional information such as database lock date. See Exhibit 159, page 2. Study L_8905, also listed as L-8905, was not on either the (b) (4) or (b) (4) lists. See Exhibits 159 and 161. It was not known if studies L_8392 or L_8905 were included in any Annual Report for Elitek as review only extended back to July 2007 and not all key study dates were included in the listings provided.

Eloxatin

NDA Annual Reports for Eloxatin (oxaliplatin injection), NDA 21-759, periods of January 31, 2006 – January 30, 2007, January 31, 2007 – January 30, 2008, January 31, 2008 – January 30, 2009, and January 31, 2009 – January 31, 2010 were reviewed. These were all the NDA Annual Reports submitted by the firm as the NDA was approved on January 31, 2005. There were no clinical studies included in the NDA Annual Report for the period of January 31, 2006 – January 30, 2007. See Exhibit 166. For the period of January 31, 2007 – January 30, 2008, one study, ARD 5099, was reported as a completed unpublished clinical trial and no ongoing other postmarketing studies were listed. See Exhibit 167. One completed unpublished clinical trial and four ongoing other postmarketing studies were listed in the NDA Annual Report, period of January 31, 2008 – January 30, 2009. See Exhibit 168.

The NDA Annual Report for Eloxatin, NDA 21-759, period of January 31, 2009 - January 31, 2010, was submitted on March 30, 2010 (Exhibit 80). The cover letter stated that the annual report did not include studies that are only required to be submitted in accordance with 21 CFR 312.33, IND annual reports. This NDA Annual Report included Clinical Study Reports dating back to at least 2002 as completed unpublished clinical trials. See Exhibit 80, page 4 to 8. Selected sections of the articles and clinical study reports reported as completed unpublished clinical trials were requested and are attached as Exhibits 81 to 112.

NDA Annual Reports for Eloxatin (oxaliplatin for injection), NDA 21-492, periods of August 9, 2006 - August 8, 2007, August 9, 2007 – August 8, 2008, and August 9, 2008 – August 8, 2009 were also reviewed. Although the firm stopped marketing oxaliplatin for injection after oxaliplatin injection was approved, the NDA for oxaliplatin for injection (NDA 21-492) is still active. There were no clinical trials reported in the NDA Annual Report for the period of August 9, 2006 – August 8, 2007. See Exhibit 169. However, both completed unpublished clinical trials and ongoing postmarketing studies were included in the next two NDA Annual Reports submitted. See Exhibits 170 and 171.

Study listings from [redacted] (b) (4) were requested and reviewed against studies included in the NDA Annual Reports. They were provided and are attached as Exhibit 172. A revised [redacted] (b) (4) listing was subsequently provided to me on May 7, 2010. See Exhibit 173. The previous version had a filter applied so that only solicited studies were included.

Two studies on the revised [redacted] (b) (4) listing were OXALI_L_00737 and OXALI_L_00869 (Exhibit 173, bottom of page 4). They were not listed in any of the NDA Annual Reports reviewed for either Eloxatin NDA as either ongoing postmarketing studies or completed clinical trials. The start date for study OXALI_L_00737 was July 1, 2006 and the end date was October 15, 2008. Study dates for OXALI_L_00869 were from February 5, 2007 through November 20, 2007. OXALI_L_00737 was

a postmarketing surveillance study done by the affiliate in (b) (4). See Exhibit 174. OXALI_L_00869 was a product registry study done by the affiliate in (b) (4) See Exhibit 175.

Study PM_L_0239, an IND study conducted in the US, was initiated in March 2006 (Exhibits 172, page 3 and 173, page 5). It was reported in IND Annual Reports on February 14, 2008 (Exhibit 176, pages 7, 14, and 15), February 17, 2009 (Exhibit 177, pages 11, 12, and 16) and February 23, 2010 (Exhibit 178, pages 7 and 10) as an ongoing study. It was not included in the NDA Annual Reports for NDA 21-492, for the period of August 9, 2006 - August 8, 2007, or for NDA 21-759, for the periods of January 31, 2006 - January 30, 2007 or January 31, 2007 - January 30, 2008 (Exhibits 166, 167, and 169). This study was submitted in the NDA Annual Reports, NDA 21-492, for the periods of August 9, 2007 - August 8, 2008 and August 9, 2008 - August 8, 2009 as an ongoing postmarketing study (Exhibits170, page 12, and 171, page 7). It was also listed as a completed unpublished clinical trial in the NDA Annual Report, NDA 21-492, for the period of August 9, 2007 - August 8, 2008 (Exhibit 170, page 3). It was submitted again in the NDA Annual Report, NDA 21-759, for the period of January 31, 2009 - January 30, 2010 as an ongoing postmarketing study (Exhibit 80, page 9).

Studies EFC-7127, L_9570, OXALI_L_01376, OXALI_L_ 03917, and PML_0098 were included on the (b) (4) listing (Exhibit 173, page 1, 4, and 5). Although the (b) (4) listing indicated that they were ongoing during the reporting periods, they were not listed in either the NDA Annual Reports for NDA 21-492, for the period of August 9, 2006 - August 8, 2007 (Exhibit 169), or NDA 21-759, periods of January 31, 2006 - January 30, 2007 and January 31, 2007 - January 30, 2008 (Exhibits 166 and 167). Instead they were submitted to the NDA Annual Reports, NDA 21-492, for the period of August 9, 2007 - August 8, 2008 (Exhibit 170) and/or NDA 21-759, for the period of January 31, 2008 - January 30, 2009 (Exhibit 168).

Study EFC-7127 was subsequently submitted as a completed unpublished clinical trial in the NDA Annual Report, NDA 21-759, period of January 31, 2009 – January 30, 2010 (Exhibit 80, page 10). This study was conducted in (b) (4) from February 2000 through October 2008. The Clinical Study Synopsis dated September 28, 2009 was submitted and is attached as Exhibit 85. Since the primary Phase I and II study objectives were to determine the (b) (4) (b) (4) I asked if this was a safety study. On May 12, 2010, the firm provided a written response that it was a safety study but not a postmarketing safety commitment. See Exhibit 179.

Ketek

NDA Annual Reports for Ketek (telithromycin tablets), NDA 21-144, were reviewed for the periods of April 1, 2007 – March 31, 2008 and April 1, 2008 – March 31, 2009. Three completed unpublished clinical trials were included in the NDA Annual Report, period April 1, 2007 – March 31, 2008 (Exhibit 180). There was no Status of Other Postmarketing Studies section, 1.13.13 (Exhibit 182). Ms (b) (6) explained that for NDA Annual Reports submitted in (b) (4) format, this section is not included. Previously the section was included with a statement that there

were no studies to report. There were no completed unpublished clinical trials included in the NDA Annual Report, period of April 1, 2008 – March 31, 2009, only three preclinical studies. See Exhibit 181.

Study listings from (b) (4) were requested and reviewed. See Exhibit 183. Then on May 7, 2010, a revised (b) (4) listing was provided as the previous listing only showed solicited studies. See Exhibit 184.

Study TELIT_L_05072 was the last study listed on the revised (b) (4) listing. Study dates were August 29, 2008 through April 30, 2009 with a Report/Result date planned for January 15, 2012. The objective was listed as Safety (incidence of each ADR). See Exhibit 184, page 7. This study was not listed in either of the NDA Annual Reports I reviewed for Ketek although it was conducted during that time. Therefore it was not reported to NDA Annual Reports. The Global Medical Affairs Template for this study was provided. It was a retrospective product registry study done by the (b) (4) affiliate. See Exhibit 185.

Discussion with Management:

The firm did not comment during the closeout meeting. However, during the inspection, Mr. Audet said that it was an oversight that Elitek study RASBU_L_00351 was not submitted. He said that he was not sure when it was added to the (b) (4) database. He said that if a study was in the (b) (4) database in April 2008, then US RAMP would have included it in the NDA Annual Report.

Prior to the closeout meeting, Mr. Audet and Ms. (b) (6) provided updated Quality Documents for NDA Annual Reports and a Clinical Trial Decision Process 2010. See Exhibits 108 to 212. It should be noted that the revised NDA Annual Reports SOP state that studies conducted under a sanofi-aventis IND as being out of scope. See Exhibit 208, page 8. The NDA Annual Reports and General Discussion with Management, item no. 4, sections of this report include additional discussion with the firm during the inspection.

OBSERVATION 2

An annual report did not include summaries of completed, unpublished clinical trials conducted by, or otherwise obtained by, the applicant.

Specifically, completed unpublished clinical trials were submitted late to NDA Annual Reports as they were not submitted in the reporting periods they were completed. Starting around April 2008, retrospective reporting was initiated to include clinical trials not previously reported to NDA Annual Reports as safety studies or postmarketing study commitments and/or to the IND. Some examples of completed clinical trials reported late are:

Ambien (zolpidem tartrate) CIV Tablets, NDA 19-908

Studies PM_L_0166 and PM_L_0167 were not submitted in the NDA Annual Report for the time period of December 16, 2006 - December 15, 2007 and December 16, 2007 - December 15, 2008. They were included in the NDA Annual Report for the time period of December 16, 2008 - December 15, 2009.

Apidra (insulin glulisine injection), NDA 21-629

Study HMR1964A/1503 was not submitted in the NDA Annual Report for the time period April 16, 2007 - April 15, 2008. It was included in the NDA Annual Report for the time period of April 16, 2008 - April 15, 2009.

Eloxatin (oxaliplatin injection), NDA 21-759, and Eloxatin (oxaliplatin for injection), NDA 21-492

Studies CU OVARY, L_9135, and L_9444 were submitted in the NDA Annual Report, NDA 21-492, for the period of August 9, 2007 - August 8, 2008 and also to the NDA Annual Report, NDA 21-759, for the period of January 31, 2009 - January 30, 2010 as completed unpublished clinical trials. They were not included in previous NDA Annual Reports for either NDA-492, for the period of August 9, 2006 - August 8, 2007 or NDA 21-759, for the periods of January 31, 2006 - January 30,2007, January 31, 2007- January 30, 2008 or January 31, 2008 - January 30, 2009 as either ongoing postmarketing studies or completed unpublished clinical trials.

Study L_8479 was submitted to the NDA Annual Report 21-492 for the period August 9, 2008 - August 8, 2009 as a completed unpublished clinical trial. It was not included in previous NDA Annual Reports for the periods of August 9, 2006 - August 8, 2007 and August 9, 2007 - August 8, 2008 as either an ongoing postmarketing study or completed unpublished clinical trial.

Studies L_9202, L_9326, and R_9262 were submitted to the NDA Annual Report, NDA 21-759, for the period of January 31, 2009 - January 30, 2010 as completed unpublished clinical trials. They were not listed in previous NDA Annual Reports for NDA 21-759 dating back to January 31, 2006 or for NDA 21-492 dating back to August 9, 2006 as either ongoing postmarketing studies or completed unpublished clinical trials.

Reference: 21 CFR 314.81(b)(2)(vi)(b)

Supporting Evidence and Relevance:

Ambien

The last three NDA Annual Reports submitted for Ambien (zolpidem tartrate) CIV tablets, NDA 19-908, were reviewed. Study listings from the [redacted (b) (4)] databases were also requested. Listed studies were compared with those included in the NDA Annual Reports.

Studies PM_L_0166 and PM_L_0167 were included on the [redacted (b) (4)] listings. Both were US studies. Study PM_L_0166 was conducted from February 15, 2006 to June 28, 2007. Study PM_L_0167 was done from February 14, 2006 to January 11, 2007. The report dates for these completed studies

were December 10, 2007 and August 28, 2007. See Exhibits 145 and 146, page 2. Although they were not IND studies, they were included in IND Annual Reports submitted on September 14, 2007 and September 12, 2008. See Exhibit 149, pages 7, and 12 to 15, and Exhibit 150, pages 9 to 11. The Final Study Protocol for PM_L_0166 lists IND # 25,361 on its cover page. See Exhibit 188, page 1. These two studies were not submitted in the NDA Annual Report for the time periods of December 16, 2006 - December 15, 2007 and December 16, 2007 - December 15, 2008 as either ongoing postmarketing or completed unpublished studies. See Exhibits 141 and 142. They were included in the NDA Annual Report for the time period of December 16, 2008 - December 15, 2009 as completed unpublished clinical trials. See Exhibit 143, pages 2 and 3. The Clinical Study Reports were also submitted. See Exhibit 143, pages 12 to 26.

Apidra

The last two NDA Annual Reports submitted for Apidra (insulin glulisine injection), NDA 21-629, were reviewed. Study listings from the (b) (4) databases were also requested. Listed studies were compared with those in the NDA Annual Reports.

Study HMR1964A/1503 was on the (b) (4) listings. Study dates were from January 4, 2005 to January 13, 2006 on the (b) (4) listing (Exhibit 130, page 6) and May 26, 2005 to March 20, 2006 on the (b) (4) listing (Exhibit 133, page 2) The Report/Result date for this pharmacokinetic (PK)/pharmacodynamic (PD) study was December 11, 2007. It was not submitted in the NDA Annual Report for the time period April 16, 2007 - April 15, 2008 (Exhibit 131). It was included in the NDA Annual Report for the time period of April 16, 2008 - April 15, 2009 (Exhibit 132, pages 1 and 13). Therefore it was submitted late to the NDA Annual Report.

Study HMR1964A/1503 was an IND study. It was in the IND Annual Report, period June 2, 2007 – June 1, 2008. Study dates were listed as June 2004 to February 2006. See Exhibit 186, pages 1, 7 and 8. It was also included in the IND Annual Report, period June 2, 2007 – June 1, 2008 with the Study Status of CSR completed. See Exhibit 187, pages 1, 12 and 13.

Eloxatin

All four NDA Annual Reports submitted for Eloxatin, NDA 21-759, and the last three NDA Annual Reports submitted for Eloxatin, NDA 21-492, were reviewed. Study listings from the (b) (4) and (b) (4) databases were requested. Listed studies were compared with those in the NDA Annual Reports.

CU OVARY was a compassionate use study conducted in (b) (4) from January 21, 2005 to October 31, 2007. The Report/Result date was in October 2008. See Exhibit 173, page 1. Study L_9135 was an observational study done in the (b) (4) from April 1, 2004 to October 30, 2006. The Report/Result date was listed as December 16, 2009. See Exhibit 173, page 4. Study

L_9444 was a Phase IV study done in the US from February 8, 2005 through July 27, 2007. It was not an IND study. The Report/Result date was listed as November 9, 2009. See Exhibit 173, page 4.

These three studies (CU OVARY, L_9135, and L_9444) were submitted in the NDA Annual Report, NDA 21-492, for the period of August 9, 2007 - August 8, 2008 (as ongoing postmarketing studies or completed unpublished clinical trials) and then to the NDA Annual Report, NDA 21-759, for the period of January 31, 2009 - January 30, 2010 as completed unpublished clinical trials (Exhibits 170 and 80). They were not included in previous NDA Annual Reports for either NDA-492, for the period of August 9, 2006 - August 8, 2007 or NDA 21-759, for the periods of January 31, 2006 - January 30, 2007, January 31, 2007- January 30, 2008 or January 31, 2008 - January 30, 2009 as either ongoing postmarketing studies or completed unpublished clinical trials. Clinical Study Report (CSR) synopses were submitted for studies L_9135, and L_9444 but not for CU OVARY in the NDA Annual Report, period of January 31, 2009 – January 30, 2010. See Exhibits 100 and 104.

Study L_8479 was done in (b) (4) from June 12, 2002 to March 2, 2007. The (b) (4) listing states that the Report/Result planned date is June 30, 2010. See Exhibit 173. This study was submitted to the NDA Annual Report 21-492 for the period August 9, 2008 - August 8, 2009 as a completed unpublished clinical trial, status of Database Locked. See Exhibit 171, pages 2 and 171. It was not included in previous NDA Annual Reports for the periods of August 9, 2006 - August 8, 2007 and August 9, 2007 - August 8, 2008 as either an ongoing postmarketing study or completed unpublished clinical trial. See Exhibits 169 and 170.

Study L_9202 was done in (b) (4) from July 3, 2004 to November 27, 2006. Study L_9326 was conducted in (b) (4) from October 15, 2004 through October 25, 2007. See Exhibit 173, page 4. Study R_9262 was done in (b) (4) from August 13, 2004 to December 2, 2006. See Exhibit 173, page 5. These three studies were submitted to the NDA Annual Report, NDA 21-759, for the period of January 31, 2009 - January 30, 2010 as completed unpublished clinical trials (Exhibit 80, pages 1 and 11). Clinical Study Report synopses were submitted with the NDA Annual Report and are attached as Exhibits 102, 103 and 112. These three studies (L_9202, L_9326, and R_9262) were not listed in previous NDA Annual Reports for NDA 21-759 dating back to January 31, 2006 or for NDA 21-492 dating back to August 9, 2006 as either ongoing postmarketing studies or completed unpublished clinical trials (Exhibits 166 to 171).

Since the Clinical Study Report Synopsis for study R_9262 lists the objectives as "(b) (4) (b) (4) (b) (4) (Exhibit 112, page 3), I asked the firm is this was a safety study. On May 12, 2010, the firm said that it was a safety study but not a postmarketing safety commitment. See Exhibit 179.

Discussion with Management:

The firm did not comment at the closeout meeting. The NDA Annual Reports and General Discussion with Management, item no. 4, sections of this report include discussion with the firm during the inspection.

OBSERVATION 3

Not all adverse drug experiences that are both serious and unexpected have been reported to FDA within 15 calendar days of initial receipt of the information.

Specifically, approximately 185 initial 15-day reports were submitted late for the time period of January 1, 2009 to March 31, 2010. About 22% of these late 15-day reports were at least 30 days late. Overall, 8846 initial and follow-up 15-day reports were submitted during this time period with around 3.5% being reported late. Approximately 60% of all late 15-day reports were foreign reports. The following are examples of initial 15-day reports that were submitted late to FDA.

Product	Mfr. Control No.	Date Received By Mfr.	Date Sent to FDA	Days Late
Glyburide	200916879GDDC	1/18/2007	7/17/2009	896 *
Glibenclamide	200916952GDDC	4/3/2007	7/20/2009	824 *
Glibenclamide	200919278GDDC	5/25/2007	8/27/2009	810 *
Furosemide	200911209EU	2/4/2008	3/17/2009	392
Eligard	A03200803546	9/8/2008	2/4/2009	134
Allegra D	200914109US	2/20/2009	5/15/2009	69
Apidra	200918792GDDC	6/10/2009	8/19/2009	55
Multaq	D01200903859	9/15/2009	1/20/2010	112
Multaq	A03200905053	10/28/2009	1/15/2010	64
Amaryl	2009SA011907	11/24/2009	1/8/2010	30
Plaquenil	2009SA006087	12/1/2009	2/3/2010	49
Lovenox	2009SA007588	12/4/2009	1/25/2010	37

* Received late from Business Partner

Reference: 21 CFR 314.80(c)(1)(i)

Supporting Evidence and Relevance:

Dr. Rullo provided an overview of late 15-day reports. See Exhibit 43, page 2. 8846 initial and follow-up 15-day reports were submitted during this time period with around 3.5% being reported late. Approximately 60% of all late 15-day reports were foreign reports. Although foreign cases are

reported to the FDA by the US affiliate, they are not received at this location. They are initially received and processed by one of two GPE departments in France or at another location in Bridgewater, NJ. GPE then forwards the cases to US Pharmacovigilance at the US affiliate (sanofi-aventis US LLC) where they are assessed for expectedness against the US label and then submitted to FDA, as required.

There were 185 initial 15-day late reports for the time period of January 1, 2009 through March 31, 2010. About 22% of these late 15-day reports were at least 30 days late. As discussed in the 15-Day Report section of this report, the firm provided multiple listings of late 15-day reports. The final listings provided are dated April 26, 2010 and are attached as Exhibits 45, 46 and 47. As discussed in the 15-Day Reports section of this report, many cases chosen for review from the initial listings of 15-day late submissions were not truly late and are not discussed in this section. The following is an overview of 15-day reports identified as being late by the firm and included on the FDA 483 as examples:

Case # (Manufacturer Control) 200916879GDDC involved glyburide (glibenclamide). This was a spontaneous case involving hospitalization reported in the medical literature and initially forwarded by Roche Products Ltd., their license partner on June 19, 2009 via email. See Exhibit 189 including pages 12 to 29. It was reported to FDA on July 17, 2009 for NDA 17-532, 896 days late. See Exhibit 189, page 2. The Medwatch form stated that the case was initially received on January 18, 2007 and was updated as a result of retrospective review involving literature cases received from November 13, 2006 through July 2, 2007. It also said that these cases were noted not to be in alignment with a Roche policy change. See Exhibit 189, page 4.

Cases # 200916952GDDC and 200919278GDDC were also glibenclamide literature cases involving hospitalization initially forwarded by Roche Products Ltd., their license partner on June 19, 2009 via email. See Exhibits 190 and 191. Case # 200916952GDDC was reported to FDA on July 20, 2009, 824 days late. See Exhibit 190, page 2. Case # 200919278GDDC was reported to FDA on August 27, 2009, 810 days late. See Exhibit 191, page 2.

It should be noted that these three glyburide (aka glibenclamide) cases received from Roche were submitted to and initially handled by Global Pharmacovigilance (GPE), Bridgewater, NJ, not US Pharmacovigilance in the US Affiliate. Following initial receipt from their business partner Roche on June 19, 2009, they were not processed within 15 calendar days as they were submitted on July 17, 2009, July 20, 2009, and August 27, 2009.

The files for these three cases received from Roche included a dated June 19, 2009. It that stated literature cases with fatal outcome events had been updated as a result of the retrospective application of a Roche policy. It also said in part '(b) (4)

(b) (4)

[redacted] See Exhibit 189, page 20.

Case # 200911209EU involved furosemide and was received from a physician via a Health Authority in Spain on February 4, 2008. It was entered in the [redacted] database. When the PSUR was being prepared in March 2009, it was found that this case should have been entered in the [redacted] database. Dr. Rullo said that one of their legacy companies had a generic furosemide and this is why it was able to be entered in [redacted] It was reported to FDA on March 17, 2009, 392 days late. See Exhibit 192.

Case # A03200803546 was a US case involving Eligard and initially received on September 8, 2008 by [redacted] one of their call centers. (Exhibit 193) The reason the firm provided for lateness was late submission. It was reported to the FDA on February 4, 2009 as a 15-day report, 134 days late. See Exhibit 46, page 1.

Case # 200914109US was a US report for Allegra D 12 Hour. A sales representative received information from a physician on February 20, 2009 and reported it late. When the sales representative took AE training on May 11, 2009, the sales representative realized it was handled incorrectly and reported the case. This case was then reported to the FDA on May 15, 2009, 69 days late. See Exhibit 194 including page 9.

Case # 200918792GDDC was a spontaneous case for Apidra from India reported by a physician to the local affiliate on June 10, 2009. See Exhibit 195, including pages 2 to 10. After review of the case by GPE in Bridgewater, NJ, it was upgraded to serious (Exhibit 195, page 23). It was then reported to the FDA as a 15-day report on August 19, 2009, 55 days late. See Exhibit 195, pages 38 and 39.

Case # D01200903859 was a Multaq clinical study case with information received from June 8 to September 15, 2009. See Exhibit 196. Although the report date on the CIOMS form was September 15, 2009 and stated it was a Study Follow-up report, the firm provided documentation showing that the initial paper submission to FDA was done on January 20, 2010 (Exhibits 196, page 2, Exhibit 197 and 47, page 2), 112 days late.

Case # A03200905053 was a US spontaneous Multaq case received from a nurse via a sales representative. The sales representative reported it on October 28, 2009. This case was a late submission. It was an initial paper submission sent to FDA on January 15, 2010. See Exhibits 198 and Exhibit 47, page 2.

Case # 2009SA011907 was an Amaryl spontaneous case that occurred in Germany. It was received from a business partner on November 24, 2009. See Exhibit 199. This case was submitted to FDA

as a 15-day report on January 8, 2010, 30 days late. The actual submission date is shown on the (b) (4) submission printout (Exhibit 199, page 2). The reason the firm provided for lateness was listed as "Late entry". See Exhibit 45, page 2.

Case # 2009SA006087 was a Plaquenil report that occurred in Australia. Initial information from a physician at the affiliate was received on December 1, 2009. See Exhibit 200. There were delays in submitting this case to US Pharmacovigilance so late submission was the reason for lateness (Exhibit 45, page 3). This case was submitted to FDA as a 15-day report on February 3, 2010. The actual submission date is shown on the (b) (4) submission printout (Exhibit 200, page 13).

Case # 2009SA007588 was a Lovenox report that occurred in the US. Initial information was received from the spouse of the patient on December 4, 2009. Upon internal review on January 21, 2010, this case was upgraded to serious and submitted to the FDA as a 15-day report on January 25, 2010, 37 days late. See Exhibit 201.

Discussion with Management:

The firm did not comment at the closeout meeting. The 15-Day Reports section of this report includes discussion with the firm during the inspection regarding late reports.

OBSERVATION 4

Follow-up reports were not submitted within 15 calendar days of receipt of new information concerning post marketing 15-day reports.

Specifically, approximately 127 15-day follow-up reports were submitted late for the time period of January 1, 2009 to March 31, 2010. About 35% of these 15-day follow-up reports were at least 30 days late. The following are examples of 15-day follow-up reports which were submitted late to FDA:

Product	Mfr. Control No.	Date Received By Mfr.	Date Sent to FDA	Days Late
Furosemide	200910549FR	1/15/2009	6/30/2009	151
Ambien	A03200902916	7/10/2009	2/24/2010	214
Lantus	200917792US	10/23/2009	3/2/2010	115
Lantus	200915406US	10/28/2009	3/2/2010	110
Lovenox	200812498US	4/18/2008	12/21/2009	597

Reference: 21 CFR 314.80(c)(1)(ii)

Supporting Evidence and Relevance:

Dr. Rullo provided an overview of late 15-day reports. See Exhibit 43, page 2. 127 15-day follow-up reports were submitted late for the time period of January 1, 2009 to March 31, 2010. About 35% of these follow-up reports were at least 30 days late. As discussed in the 15-Day Report section of this report, the firm provided multiple listings of late 15-day reports. Listings of follow-up late reports dated April 23, 2010 were provided and are attached as Exhibit 44, pages 3, 6 and 7. The final listings provided are dated April 26, 2010 and are attached as Exhibits 45, 46 and 47. As discussed in the 15-Day Reports section of this report, many cases chosen for review from the initial listings of 15-day late submissions were not truly late and are not discussed in this section. The following is an overview of 15-day follow-up reports identified as being late by the firm and included on the FDA 483 as examples:

Case # 200910549FR was a furosemide (Lasilix) report involving hospitalization received on January 15, 2009 from the French Health Authority (afssaps). The Medwatch form states that during internal review at the time of PSUR preparation, the listedness for eczematous dermatitis was changed from listed to unlisted for furosemide. A 15-day follow-up report was then submitted late on June 30, 2009, 151 days late. See Exhibit 202, including the Medwatch form on pages 11 to 13.

Case # A03200902916 was an Ambien report involving the termination of a pregnancy following drug exposure. This report was initially received from a pharmacist in the US on July 10, 2009. See Exhibit 203. The Medwatch form states that after internal review on February 18, 2010, the seriousness criteria were corrected to add death. See Exhibit 203, page 16. Previously the outcome was an important medical event. A 15-day follow-up report was then submitted late on February 24, 2010, 214 days late. The [redacted] (b) (4) Submission documents the date sent to FDA on February 24, 2010. See Exhibit 203, page 11.

Case # 200917792US was a Lantus report initially received from a consumer in the US on August 31 and September 1, 2009. Additional information was received from a consumer on October 23, 2009 but was not submitted as a 15-day follow-up until March 2, 2010. See Exhibit 204. The [redacted] (b) (4) Submission documents the date sent to FDA on March 2, 2010. See Exhibit 204, page 4. The reason for lateness provided by the firm was Late Entry. See Exhibit 45, page 3.

Case # 200915406US was a Lantus report initially received from a consumer in the US on June 17, 2009. See Exhibit 205. A Medwatch form states that on October 28, 2009, additional information was received from a nurse but not submitted to the FDA as a follow-up report until March 2, 2010. As previously discussed in this report and due to issues with data from [redacted] (b) (4) migrated to [redacted] (b) (4) block G of this Medwatch form states that this is the Initial 15-Day rather than a 15-Day

follow-up. Also there is an inaccurate receipt date of June 17, 2009, the initial awareness date, not the actual awareness date for receipt of additional information. See Exhibit 205, pages 23. The (b) (4) AERS E2B Submission printout shows that this follow-up report was sent to FDA on March 2, 2010. See page 8 of Exhibit 205.

Case # 200812498US was a Lovenox report initially received from a nurse in the US on April 18. 2008. See Exhibit 76. Upon internal review on December 11, 2009, it was determined that some information previously received in April 2008 was erroneously left out of the case. A 15-day follow-up report was then submitted to FDA on December 21, 2009, 597 days late. The AERS E2B Submission printout shows that this follow-up report was sent to FDA on December 21, 2009. See Exhibit 76, page 7. As with case # 200915406US, Block G of the Medwatch form states that this is an initial 15-day report rather than a follow-up 15-day report due to issues with data from (b) (4) migrated to (b) (4)

Discussion with Management:

The firm did not comment at the closeout meeting. The 15-Day Reports section of this report includes discussion with the firm during the inspection regarding late reports.

Mr. Audet and Dr. Rullo said that the firm would respond to the FDA 483 in writing and asked if the response should be submitted within 15 calendar days or 15 business days. I said that any response they submit should be within 15 business days. Dr. Chew said that the firm has already started proactive actions and will take every measure possible to remediate the findings.

REFUSALS

There were no refusals during the inspection.

GENERAL DISCUSSION WITH MANAGEMENT

Discussion with management and a closeout meeting was held on May 13, 2010. sanofi-aventis staff present were as follows:

Paul H. Chew, MD, US Chief Science Officer/Chief Medical Officer
Craig Audet, Vice President, US Regulatory Affairs Marketed Products
Patrick Caubel, MD, Vice President, Global Pharmacovigilance & Epidemiology
Rosalina Domin, Senior Director, Case Management, US Pharmacovigilance
Tsilla Elhadad, MD, Associate Vice President, Global Pharmacovigilance & Epidemiology, PRCU

(b) (6), Senior Manager, Regulatory Submissions, US Regulatory Affairs Marketed Products
Linda Scarazzini, MD, Associate Vice President, US RISC, Drug Safety
Barbara Rullo, MD, Vice President, Drug Safety
Karen Simpson, MD, Senior Director, Resources and Projects, US Pharmacovigilance
Katy Sotirov, Associate Vice President, Quality Systems and Support
Peter Thome, Senior Director, Local User Support, Quality & Compliance

The following inspectional findings, not included on the FDA 483, were discussed with the firm during the inspection and at the closeout meeting:

1) Clinical Study Databases:

Data from the (b) (4) clinical study databases are used for NDA Annual Reports. These databases are also used to obtain study information for periodic safety reports. These global databases should have accurate and complete study data if they are used for regulatory submissions.

Key study dates such as First Patient First Visit (FPFV), Last Patient Last Visit (LPLV), Database Lock (DBL) and Clinical Study Report (CSR) were not always on the reports generated from these databases, primarily with (b) (4) listings. (b) (4) listings for Eloxatin and Ketek are examples of this. See Exhibits 172, pages 2 to 8, and 183, pages 1 to 5.

Some clinical studies were on both the (b) (4) listings. For example, there were some Apidra studies including HMR 1964A/3508, HMR 1964A/3511, HMR 1964A/3515, HMR 1964A/4002 and APIDRA_C_ 2083 on both lists. See Exhibits 130 and 133, page 2. The firm said that this occurred when responsibility for the study was transferred. Study dates fields were not completed in (b) (4) database but they did appear in (b) (4) listings. Eloxatin study L_9444 was included on the (b) (4) listing with a status of database lock on October 23, 2008. See Exhibit 172, page 4. The (b) (4) listing indicates that the Global Status is Reported-Archived and that it was a prematurely terminated study. See Exhibit 173, page 4. Eloxatin study L_9444 was listed in Eloxatin NDA Annual Report, NDA 21-759, period January 31, 2009 – January 30, 2010 (Exhibit 80) and a CSR synopsis included (Exhibit 104).

No issues were found with postmarketing commitment studies being addressed and not included in NDA Annual Reports. However, two Eloxatin postmarketing commitment studies, EFC 7462 and EFC 7112, did not appear on either the (b) (4) lists provided. See Exhibits 172 and 173. These two studies were referenced in both the NDA approval and a supplemental NDA approval letters for Eloxatin, NDA 21-492 dated August 9, 2002 and January 9, 2004. See Attachment 7 and 8.

The firm did not comment at the closeout meeting. However, prior to the closeout meeting, the firm provided an Action Plan for Clinical Trial Tracking Database Data Reliability and Completeness Actions. It lists three action plans. They were summarizing the current status of controls in place, performance of a system audit to assess the compliance in view of regulatory actions, and elaboration of further actions based on the results of the summary and audit. It is attached as Exhibit 207. Additional discussion with the firm regarding their clinical study databases is included in the NDA Annual Reports and Voluntary Corrections sections of this report.

2) Computer System Validation (CSV) of (b) (4) AERS

The computer system validation for the (b) (4) AERS was done by GPE. This application was released into production on November 9, 2009 using an Interim Validation Report (IVR) that is still not a final Validation Report.

There were a number of deferred issues listed in the Interim Validation Report that were not resolved and/or finalized such as the Traceability Matrix A 21 CFR Part 11 requirement included in the Traceability Matrix was that data be in human readable format throughout the retention period. The Traceability Matrix stated this functionality was not available. Dan Sum from GPE said that this was a mistake and that the functionality was available.

During validation, the Neg Ack script could not be done in the FDA testing environment. After I asked about this, email messages were subsequently provided concerning this. However, this was not formally documented in the validation files such as note to the file or change in plan. I said that personal email messages may not be retained and this information may be lost.

On or around December 2, 2009, No ACKS were received from the FDA for at least 184 cases and there were some late 15-day reports. Specifically, there were E2B transmission failures and these cases were not properly acknowledged as being received by FDA. It was subsequently determined that a No ACK query report needed to be run daily to detect these issues. I said I had concerns about the adequacy of testing done during validation to detect these types of issues and about GPE's checks in the production environment after (b) (4) was in production. Mr. Thome said that the US affiliate is now doing daily checks. A Work Instruction was in draft to reflect the daily checks and was finalized during the inspection.

I said that for some validation test scripts, lines were drawn through each step rather than each step being initialed and dated when done. I said that this was not a good documentation practice

There was a clock date issue with Medwatch forms. For certain cases initially entered in (b) (4) and then follow-up information is entered in (b) (4) the first awareness date is displayed on the Medwatch form in section G4 (Date received by manufacturer), not the date of receipt for follow-up

information. In addition, these Medwatch forms print as Initial 15-Day Reports, not Follow-Up Reports.

At the closeout meeting, Dr. Caubel said that from the global standpoint, they are aware of weaknesses in the validation processes and they are reinforcing this with staff. He said that they may bring in additional validation specialists to the organization. He said that they relaunched a task force to close issues within 90 days. He said that a contract with the consultant, Accenture, has been signed.

The (b) (4) AERS (AE Reporting System) section of this report includes additional discussion with the firm regarding the computer system validation and issues that have arisen. It also references related Exhibits for documentation obtained during the inspection.

3) Reporting Tools

There is no compliance monitoring tool in (b) (4) yet to identify 15-day late reports and assist in follow-up. This is not an FDA requirement. However, when a monitoring tool was available here for (b) (4) the Quality group was proactive and Corrective and Preventive Actions (CAPAs) were done for cases under their control (US cases). In 2007, only 88% of cases were submitted to the FDA on time. After proactive monitoring was initiated with follow-up actions, the on time submission rate increased to 99.61% in 2008 and 99.58% in 2009.

I commented that I reviewed many cases that not truly late as the late 15-day report listings initially provided to me contained many cases that were not truly late.

Dr. Rullo said that a team was set up. She said that they are putting a prospective and retrospective tool together. This will help prevent late cases and learning from cases that are late. An (b) (4) Compliance Proactive Monitoring Plan was provided prior to the conclusion of the inspection. It states that a monitoring system will be built to support the new (b) (4) database. See Exhibit 206.

4) NDA Annual Reports

The following findings, not included on the FDA 483, relate to retrospective reporting of clinical studies in NDA Annual Reports.

Some clinical trials for Apidra were reported twice to the NDA Annual Reports as completed unpublished clinical trials. For example, studies HMR1964A_3511 and HMR1964A_3514 were listed in NDA Annual Periods for both the periods of April 16, 2007 – April 15, 2008 and April 16,

2008 – April 15, 2009 as completed unpublished clinical trials. See Exhibit 131, pages 12 and 15, and Exhibit 132, pages 12 and 13.

Some Eloxatin studies were reported to one NDA and later reported to the other Eloxatin NDA. For example, studies OXALI_L_04037 and OXALI_L_03917 were reported to the NDA Annual Report, NDA 21-492, period of August 9, 2008 – August 8, 2009 (Exhibit 171, pages 6 and 7). Then they were reported again to the NDA Annual Report, NDA 21-759, period of January 31, 2009 – January 30, 2010 (Exhibit 80, page 9).

The format for including studies in NDA Annual Reports was not consistent. For example, the study summary for reporting completed unpublished clinical trials varied. For the Eloxatin NDA Annual Report, NDA 21-759, period January 31, 2007 – January 30, 2008, a summary was provided for study ARD 5099 that included the study design, dose/regimen, number of patients, and a conclusion. See Exhibit 167 pages 8 and 9. In the next NDA Annual Report, only the study number, short title, full title, global status and countries were provided. See Exhibit 168, page 6.

The criteria for reporting studies as completed unpublished clinical trials varied. Mr. Audet said that now for a study to be considered completed, the Clinical Study Report (CSR) has to be approved and submitted. Previously a study was considered complete if the status was Last Patient Last Visit (LPLV), Last Patient Out (LPO) or Database Lock (DBL). However, this was not always consistent. An example is the Eloxatin NDA Annual Report, NDA 21-492, period of August 9, 2007 – August 8, 2008. Two US studies (L_9210 and PM_L_0239) were listed as completed unpublished clinical trials with the Global Status of Database Lock and Last Patient In. Three studies (CU OVARY, L_9904, and OXALI_L_01574) with the Global Status of Database Locked, Reported-Archived, and Last Patient Out were listed as ongoing other postmarketing studies. See Exhibit 170, pages 3, and 11.

The last Eloxatin NDA Annual Report submitted for NDA 21-759 was for the period of January 31, 2009 – January 30, 2010. See Exhibit 80. Clinical Study Synopses were submitted for about half the completed unpublished clinical trials. See Exhibits 81 to 112. Several of them were not translated into English. See Exhibits 92 and 105. Clinical studies that were completed before the NDA was approved were included.

Some IND studies were included in the NDA Annual Reports as part of the firm's retrospective reporting but not all were. Mr. Audet said that they included all clinical trials that were in the study databases.

At the closeout meeting, Mr. Audet said that IND studies were submitted by reference to the IND Annual Report. During the inspection, I said that the FDA expectation was that IND studies also be listed in the NDA Annual Reports.

During the inspection, Mr. Audet said that clinical study reports would be resubmitted after they were translated. He said that older studies from legacy companies may not be in the clinical study databases. He said that some older databases don't exist any longer especially prior to 2006. He said that the upper management of sanofi-aventis has directed affiliates to add local clinical studies to the (b) (4) database. He said if the study was in one of the databases at the time they started retrospective submission of studies, they included it in the NDA Annual Report. Mr. Audet said that for Eloxatin they were not sure what NDA the studies had to be reported to so to be conservative they reported to both.

5) Periodic Safety Reports

Eloxatin study ARD 5531 was submitted late to the Eloxatin PSUR. Study L9870 also appears to have been submitted late. Eloxatin studies EFC_7127 and L_9262 were not included in the PSURs reviewed. These were safety studies but not postmarketing commitment safety studies. Refer to Objectionable Conditions and Management Response, Observations # 1 and 2, for additional information on studies EFC_7127 and L_9262.

To summarize, the Eloxatin PSUR, period May 1, 2008 – April 30, 2009 listed two newly analyzed company studies, POP5347 and ARD5531. See Exhibit 102, pages 1 and 2. The PSUR states that this study was not previously presented in the correspondence reference period (PSUR No. 18). Mr. Thome said that as indicated in the PSUR, a publication discussing this study was found during a review of the literature while the PSUR was being prepared.

The study report dated February 23, 2006 for Eloxatin study ARD5531 (aka L7965 or L_7965) was included in the NDA Annual Report, NDA 21-759, period of January 31, 2009 – January 30, 2010. See Exhibit 91. This study was listed as L_7965 in the ClubNet database. See Exhibit 173, page 3. It is not known whether this study was reported previously in an Eloxatin NDA Annual Report as it was completed prior to my review period for NDA Annual Reports.

The Eloxatin PSUR, period November 1, 2008 to April 30, 2009, stated in section 7.2 that a study report was planned for study L9870 in June 2009. The objectives were stated as to assess the (b) (4) (b) (4) Exhibit 213, page 4). It was not listed in the PSURs for the periods May 1, 2008 – October 31, 2008 (Exhibit 213, page 6) or November 1, 2007 – April 30, 2008 (Exhibit 214, page 9) so it is not know if it was previously reported. It appears to have been reported late to the PSUR as the study dates in the (b) (4) atabase were March 15, 2005 to January 23, 2009. See Exhibit 173, page 4. The Extended Synopsis/Concept Sheet for this study conducted in Germany is attached as Exhibit 214. This study was reported to the Eloxatin NDA Annual Report, NDA 21-492, period of August 9, 2008 – August 8, 2009 as a completed unpublished clinical trial, status of Database Locked. (Exhibit 171, page 3). For the previous reporting period, it was listed as an ongoing postmarketing study. Although not included on the FDA 483 as a study reported late, this study was not previously

reported to the NDA Annual Report, NDA 21-492, period August 9, 2006 – August 8, 2007 (Exhibit 169).

The firm includes a list of studies initiated in Section 2, Narrative Discussion of Action Taken, in US Periodic Adverse Drug Experience Reports (PADERs). There were no studies reported in the quarterly PADER for Apidra, period October 16, 2007 – January 15, 2008. See Exhibit 137. However, they were included in the next three quarterly PADERs. See Exhibits 138 to 140. During the inspection Mr. Thome said that they are now including all studies in PADERs.

The comment did not company at the closeout meeting. However, during the inspection, Mr. Thome said that their Work Instruction is now harmonizing what studies will be included in PSURs and PADERs. Therefore, studies that may not have been previously reported will now be included.

6) Postmarketing Commitment Tracking

In a Supplement Approval letter dated October 16, 2009 for Elitek, FDA requested that the dataset for clinical trial TDU4730 be reanalyzed. This was a previously submitted pharmacokinetic (PK) and pharmacodynamic (PD) study. See Attachment 6, page 3. The commitment to reanalyze data in this study was not included in the firm's postmarketing commitment tracking sheets. See Exhibit 124. Study TDU4730 was also not included on any of listings provided during the inspection from the (b) (4) databases. See Exhibits 157 to 161.

The company did not comment at the closeout meeting. During the inspection Mr. Audet said that not including this study on the tracking list was an oversight. However, he said this commitment was addressed and he provided documentation of that. See Exhibit 218.

7) Procedural Documents

Both the Case Management group and the Affiliate Safety Officer (i.e., physicians) utilize Job Aids. They are not controlled documents as their other procedural documents are. For example, their SOPs and Work Instructions follow specific templates and are signed and approved. Some of them are attached as Exhibits 215 to 217. During the inspection both Mr. Thome and Ms. Domin said that their department had already initiated making Job Aids controlled documents.

In the Scope section of SOP No. US-PV-022, Regulatory Filing of Expedited Adverse Event Reports, it states that this SOP is applicable to OTC products that do not have an NDA. See Exhibit 22, page 3. However, this SOP or other SOPs did not state that all serious OTC products without an NDA are subject to expedited reporting whether the ADEs are expected or unexpected. However, Dr. Rullo said that this was documented in the USPV Glossary. See Exhibit 30, page 2. To clarify this requirement, the firm said that they were revising SOPs No. US-PV- 022 and US-PV-002 to

incorporate more specificity on the handling of OTC cases. Pages from draft revisions of these SOPs were provided and are attached as Exhibit 31.

The firm did not comment at the closeout meeting.

ADDITIONAL INFORMATION

N/A

SAMPLES COLLECTED

There were no samples collected during the inspection.

VOLUNTARY CORRECTIONS

As previously discussed in this report, the firm's management was cooperative and initiated corrective actions prior to the conclusion of the inspection. Corrective action plans for the firm's clinical study databases and a compliance monitoring tool to identify late 15-day reports were provided. Changes in procedural documents were either initiated or finalized. US Regulatory Affairs Marketed Products initiated changes to their SOPs for NDA Annual Reports. Revisions of several Case Management SOPs were initiated to highlight that all serious ADEs for OTC products (not covered by a NDA), not just serious unexpected ADEs, were subject to expedited reporting. A draft Work Instruction for monitoring E2B transmission failures was finalized and approved.

EXHIBITS COLLECTED

1) sanofi-aventis 2009 Annual Report sections including Directors, Business Overview and Organizational Structure (57 pages)
2) sanofi-aventis 2009 Annual Report section on management structure (16 pages)
3) List of NDA and ANDAs (4 pages)
4) Product list responsible at this site, with name on label (4 pages)
5) Current GPE product assignment list (23 pages)
6) List of NDAs withdrawn in the last 2 years (2 pages)
7) Elitek Prescribing Information (USPI) (5 pages)
8) Current Prescribing Information (USPI) for Eloxatin (17 pages)
9) USPI for Multaq (5 pages)
10) Current Prescribing Information (USPIs) for Ketek, Apidra and Ambien (59 pages)

11) USPI for Oforta (2 pages)
12) Organizational Chart for US Regulatory Affairs Marketed Products (2 pages)
13) US Organizational Chart (2 pages)
14) Executive Committee and US Medical Affairs Organizational Charts (4 pages)
15) US Drug Safety Organizational Chart (1 page)
16) Organizational Charts for Local and Corporate Compliance (21 pages)
17) R&D Quality Operations Organization Charts (12 pages)
18) Detailed Description of the Pharmacovigilance System, February 4, 2010 version (123 pages)
19) SOP No. US-REG-006, NDA Annual Reports (16 pages)
20) SOP No. US-PV-012, Organization, Roles and Responsibility of sanofi-aventis US Pharmacovigilance (9 pages)
21) Index of SOPs for local and global auditing responsibility over USPV (10 pages)
22) SOP No. US-PV-022, Regulatory Filing of Expedited Adverse Event Reports (5 pages)
23) SOP US-PV-008, Training of US Pharmacovigilance Staff (7 pages)
24) SOP US-PV-009, Pharmacovigilance Training for sanofi-aventis Employees, Contractors and Agents (7 pages)
25) SOP US-QA-067, Recall of a Marketed Product (9 pages)
26) Standard AE Reporting Form (3 pages)
27) Flowchart of Case Management Process (3 pages)
28) List of Heritage Products Handled by (b) (4) (2 pages)
29) SOP US-PV-002, Handling Unsolicited Individual Case Safety Reports for Registered/Marketed Products in the United States (10 pages)
30) USPV Glossary Page, Expedited Reporting (2 pages)
31) SOP revisions to incorporate more specificity for OTC cases (3 pages)
32) Listing of AEs for Benzalconium January 1, 2008 to present (2 pages)
33) Index of US Pharmacovigilance SOPs (3 pages)
34) Listing of late cases, 4/7/2010 version (5 pages)
35) Listing of late submissions, 4/12/2010 version (6 pages)
36) Assessment of (b) (4) cases more than 30 days late, 4/13/2010 (6 pages)
37) (b) (4) cases with reasons late or why not truly late (17 pages)
38) Multaq Late Paper Submissions (1 page)
39) Oforta Late Paper Submissions (1 page)
40) Metrics for late cases and late submissions provided 4/16/2010 (18 pages)
41) Updated (b) (4) late case list, 4/22/2010 (8 pages)
42) Updated [redacted] late case list, 4/22/2010 (8 pages)
43) Overall Compliance Data (5 pages)
44) Revised (b) (4) and (b) (4) ate case lists, 4/23/2010 (7 pages)

45) Final (b) (4) late case list, 4/26/2010 (3 pages)
46) Final [redacted] late case list, 4/26/2010 (3 pages)
47) Late paper submissions for Multaq and Oforta (4 pages)
48) (b) (4) Compliance Plan with April 2010 Submission Analysis and late cases (8 pages)
49) Dr. Patrick Caubel, GPE, presentation regarding (b) (4) 12 pages)
50) SOP US-PV-031, Compliance Monitoring in sanofi-aventis US Pharmacovigilance (5 pages)
51) Compliance monitoring with (b) (4) (6 pages)
52) Late case and CAPA report for October 2009 (5 pages)
53) CAPA for failure to update the case downgrade status (5 pages)
54) SOP US-PV-001, Preparation of Periodic Reports and PSUR Waivers for Submission to the FDA (10 pages)
55) Submission Schedule for PADERs and PSUR Waivers (7 pages)
56) GPE Policy WW-GPE-PSR-POL-001, Planning, Preparation, Distribution and Submission of Periodic Safety Reports for Registered or Marketed Products (12 pages)
57) List of late aggregate reports (2 pages)
58) SOP US-PV-003, Supporting GPE Signal Detection for Registered Products in US Pharmacovigilance (10 pages)
59) Most recent completed Local Signal Detection forms for Multaq and Oforta (3 pages)
60) (b) (4) Interim Validation Report signed November 9, 2009 (37 pages)
61) [redacted] Validation Plan (20 pages)
62) [redacted] (PVLTS) Traceability Matrix (111 pages)
63) [redacted] validation deviations status tracking sheets (8 pages)
64) Revised (b) (4) validation deviations status tracking sheets (5 pages)
65) Tracking document for (b) (4) nterim Validation Report (IVR) deviations (5 pages)
66) (b) (4) change control record for # 23048 (8 pages)
67) List of 184 cases affected by E2B transmission failure (3 pages)
68) FDA contact report for the E2B transmission failure after (b) (4) mplementation (5 pages)
69) Submission flow scripts for (b) (4) (71 pages)
70) Correspondence with FDA re: negative acknowledgement test case (5 pages)
71) Prepared documentation regarding inability to test for negative acknowledgement (2 pages)
72) Email certification from FDA for E2B (10 pages)
73) Draft process document for E2B transmission checks (7 pages)
74) Work Instruction USMA-PV-AWR-WIN-0001, Report Verification (7 pages)
75) (b) (4) training materials (5 pages)
76) Case # 200812498US Medwatch and source documents (35 pages)
77) Summary of actions to address clock date issues with (b) (4) 3 pages)
78) Local products for literature searches done by US affiliate (2 pages)

79) SOP US-PV-007, Scientific Literature Screening for sanofi-aventis Products (8 pages)
80) Eloxatin NDA Annual Report, NDA 21-759, January 31, 2009- January 30, 2010 (12 pages)
81) Request for studies in Eloxatin NDA 21-759 Annual Report, January 31, 2009 – January 30, 2010 (1 page)
82) Oxaliplatin 2008 literature article from Arch Gynecol Obstet included in Eloxatin Annual Report (6 pages)
83) Oxaliplatin Clinical Study Report synopsis, study C-8552 (6 pages)
84) Oxaliplatin Clinical Study Report synopsis, study C-8601 (8 pages)
85) Oxaliplatin Clinical Study Report synopsis, study EFC_7127 (4 pages)
86) Oxaliplatin Clinical Study Report synopsis, study EFC 7233 (5 pages)
87) Oxaliplatin Clinical Study Report synopsis, study EFC_7276 (3 pages)
88) Oxaliplatin Clinical Study Report synopsis, study EFC 7277 (5 pages)
89) Oxaliplatin Clinical Study Report synopsis, study EFC_7407 (3 pages)
90) Oxaliplatin Clinical Study Report synopsis, study EFC 7496 (5 pages)
91) Oxaliplatin Clinical Study Report synopsis, study ARD5531 (aka L7965) (9 pages)
92) Oxaliplatin study report, cover page and index, untranslated, study L8005 (2 pages)
93) Oxaliplatin Clinical Study Report synopsis, study L_8128 (3 pages)
94) Oxaliplatin Clinical Study Report synopsis, study L_8330 (3 pages)
95) Oxaliplatin 2005 abstract from Journal of Clinical Oncology (2 pages)
96) Oxaliplatin Clinical Study Report synopsis, study L_8719 (4 pages)
97) Oxaliplatin Clinical Study Report synopsis, study ARD-5099 (aka L8851) (12 pages)
98) Oxaliplatin Clinical Study Report synopsis, study L_8907 (7 pages)
99) Oxaliplatin Clinical Study Report synopsis, study L_8915 (10 pages)
100) Oxaliplatin Clinical Study Report synopsis, study L9135 (3 pages)
101) Oxaliplatin Clinical Study Report synopsis, study L_9186 (4 pages)
102) Oxaliplatin Clinical Study Report synopsis, study L_9202 (4 pages)
103) Oxaliplatin Clinical Study Report synopsis, study L-9326 (6 pages)
104) Oxaliplatin Clinical Study Report synopsis, study L_9444 (8 pages)
105) Oxaliplatin Clinical Study Report, pages 1-12, untranslated, study L9479 (12 pages)
106) Oxaliplatin Clinical Study Report synopsis, study L9904 (21 pages)
107) Oxaliplatin Clinical Study Statistical Report synopsis, study L9585 (3 pages)
108) Oxaliplatin Clinical Study Statistical Report synopsis, study L9962 (3 pages)
109) Oxaliplatin Clinical Study Report, pages 1 to 12, untranslated, study LTS7191 (12 pages)
110) Oxaliplatin Re-examination Report synopsis, study Obs 7492 (6 pages)
111) Oxaliplatin Clinical Study Report synopsis, study PM_L_0126 (9 pages)
112) Oxaliplatin Clinical Study Report synopsis, study R_9262 (8 pages)
113) Firm response on inclusion of IND studies in NDA Annual Reports (1 page)

114) Draft Work Instruction USMA-CLIN-RTP-WIN-0003, US Medical Operations Contributions to Regulatory Reports (9 pages)
115) PSUR Waivers for Arava, Elitek and Eloxatin (15 pages)
116) Waivers not to submit MedWatch forms for non-serious cases (41 pages)
117) List of Local and Global Business Partners for US marketed products (4 pages)
118) Updated Business Partner list with SDEA status (4 pages)
119) Business Partner list showing who reports to FDA (4 pages)
120) Local agreements for Oforta, Clomid and Diabeta (48 pages)
121) Sections of Clomid and Diabeta agreements with PV responsibilities (4 pages)
122) Reconciliation of cases with business partner and UCB SDEA (11 pages)
123) [redacted] (b) (4) contract (33 pages)
124) Firm response to tracking of post approval commitments with GPE Policy and US RAMP tracking sheets (96 pages)
125) USPV Adverse Event Routing Slip (2 pages)
126) Multaq REMS (62 pages)
127) Lantus PTC no. 1000367172 (4 pages)
128) SOP US-QA-020, Drug Product Quality Complaint Processing (12 pages)
129) Table of IND Annual Reports provided (2 pages)
130) Revised [redacted] (b) (4) Apidra study listing (9 pages)
131) Apidra NDA Annual Report, NDA 21-629, period April 16, 2007 – April 15, 2008 (15 pages)
132) Apidra NDA Annual Report, NDA 21-629, period April 16, 2008 – April 15, 2009 (20 pages)
133) Apidra [redacted] (b) (4) study listings (4 pages)
134) Study Outline Template for Apidra studies not in NDA Annual Reports (18 pages)
135) Table of Apidra PADERs and NDA Annual Reports provided (1 page)
136) Apidra studies in PADER January 16, 2008 – April 15, 2008 (4 pages)
137) Apidra studies in PADER October 16, 2007 – January 15, 2008 (2 pages0
138) Apidra studies in PADER July 16, 2008 – October 15, 2008 (2 pages)
139) Apidra studies in PADER October 16, 2008 – January 15, 2009 (3 pages)
140) Apidra studies in PADER January 16, 2009 – April 15, 2009 (3 pages)
141) Ambien NDA Annual Report December 16, 2006 – December 15, 2007 (7 pages)
142) Ambien NDA Annual Report December 16, 2007 – December 15, 2008 (4 pages)
143) Ambien NDA Annual Report December 16, 2008 – December 15, 2009 (51 pages)
144) Ambien [redacted] (b) (4) study listing (1 page)
145) Ambien [redacted] (b) (4) study listing (1 page)
146) Ambien Revised [redacted] (b) (4) study listing (3 pages)
147) Ambien Fina[redacted] (b) (4) study listing (3 pages)
148) Ambien Revised [redacted] (b) (4) study listing (2 pages)

149) Ambien IND Annual Report, period July 16, 2006 – July 15, 2007 (20 pages)
150) Ambien IND Annual Report, period July 16, 2007 – July 15, 2008 (21 pages)
152) Elitek Annual Report, period July 12, 2007 – July 11, 2008 (13 pages)
153) Elitek Annual Report, period July 12, 2008 – July 11, 2009 (8 pages)
154) FDA letter dated April 9, 2004 transferring Elitek to CDER from CBER (5 pages)
155) Table summarizing Elitek Annual Reports and PSURs provided (1 page)
156) Elitek screen shot for Annual Report, July 12, 2008 – July 11, 2009 (3 pages)
157) Elitek (rasburicase) (b) (4) study list (1 page)
158) Elitek (b) (4) study list (1 page)
159) Revised (b) (4) study list (2 pages)
160) Response on reason for revised Elitek (b) (4) study list (1 page)
161) Revised (b) (4) Elitek study list (3 pages)
162) Elitek (rasburicase) PSUR study section, September 1, 2007 – February 29, 2008 (2 pages)
163) Cover letter Elitek PSUR dated April 25, 2008 (1 page)
164) Medical Affairs Extended Synopsis Template, rasburicase study RASBU_L_01489 (5 pages)
165) Medical Affairs Extended Synopsis, rasburicase study RASBU_L_00351 (42 pages)
166) Eloxatin NDA Annual Report, NDA 21-759, January 31, 2006 – January 31, 2007 (6 pages)
167) Eloxatin NDA Annual Report, NDA 21-759, January 31, 2007 – January 30, 2008 (11 pages)
168) Eloxatin NDA Annual Report, NDA 21-759, January 31, 2008 – January 31, 2009 (9 pages)
169) Eloxatin NDA Annual Report, NDA 21-492, August 9, 2006 – August 8, 2007 (6 pages)
170) Eloxatin NDA Annual Report, NDA 21-492, August 9, 2007 – August 8, 2008 (15 pages)
171) Eloxatin NDA Annual Report, NDA 21-492, August 9, 2008 – August 8, 2009 (10 pages)
172) Eloxatin (b) (4) study listings (8 pages)
173) Revised Eloxatin (b) (4) study listing (6 pages)
174) Eloxatin Medical Affairs Extended Synopsis Template, study OXALI_L_00737 (4 pages)
175) Eloxatin Global/Regional Extended Synopsis, study OXALI_L_00869 (3 pages)
176) Oxaliplatin (Eloxatin) IND Annual Report, period December 19, 2006 – December 18, 2007 (16 pages)
177) Oxaliplatin IND Annual Report, period December 19, 2007 - December 18, 2008 (16 pages)
178) Oxaliplatin IND Annual Report, period December 19, 2008 – December 18, 2009 (11 pages)
179) Firm response to Eloxatin studies EFC_7127 and R_9262 being safety studies (2 pages)
180) Ketek NDA Annual Report, period April 1, 2007 – March 31, 2008 (12 pages)
181) Ketek NDA Annual Report, period April 1, 2008 – March 31, 2009 (17 pages)
182) Table summarizing Ketek PSURs and NDA Annual Reports provided (1 page)
183) Ketek (b) (4) study listings (5 pages)
184) Revised (b) (4) study listing (7 pages)
185) Ketek Study Outline Template for study TELIT_L_05072 (3 pages)

186) Apidra IND Annual Report, period June 2, 2005 to June 1, 2006 (24 pages)
187) Apidra IND Annual Report, period June 2, 2007 to June 1, 2008 (33 pages)
188) Zolpidem tartrate (Ambien) protocol PM-L-0166, pages 1 to 8 (8 pages)
189) Case # 200916879GDDC Medwatch and source documents (22 pages)
190) Case # 200916952GDDC Medwatch and source documents (24 pages)
191) Case # 200919278GDDC Medwatch and source documents (28 pages)
192) Case # 200911209EU Medwatch and source documents (35 pages)
193) Case # A03200803546 Medwatch and source documents (19 pages)
194) Case # 200914109US Medwatch and source documents (20 pages)
195) Case # 200918792GDDC Medwatch and source documents (39 pages)
196) Case # D01200903859 Medwatch and source documents (10 pages)
197) Case # D01200903859 screen print from submission page (2 pages)
198) Case # A03200905053 Medwatch and source documents (16 pages)
199) Case # 2009SA011907 Medwatch and source documents (14 pages)
200) Case # 2009SA006087 Medwatch and source documents (27 pages)
201) Case # 2009SA007588 Medwatch and source documents (28 pages)
202) Case # 200910549FR Medwatch and source documents (12 pages)
203) Case # A03200902916 Medwatch and source documents (22 pages)
204) Case # 200917792US Medwatch and source documents (7 pages)
205) Case # 200915406US Medwatch and source documents (24 pages)
206) (b) (4) Compliance Proactive Monitoring Plan (3 pages)
207) Action Plan for Clinical Trial Tracking Database (1 page)
208) Updated Quality Documents for NDA Annual Report Process (14 pages)
209) Clinical Trial Decision Process 2010 (2 pages)
210) Instructional Communication to Medical Contributors (2 pages)
211) Notification of NDA Annual Report Initiation (from NDA Annual Reports SOP) (4 pages)
212) Draft Work Instruction USMA-CLIN-RPT-WIN-0003, US Medical Operations Contributions to Regulatory Reports (8 pages)
213) Oxaliplatin Summary Bridging Report and PSUR sections, Period May 1, 2008 to April 30, 2009 (10 pages)
214) Eloxatin Study L_9870 study synopsis (10 pages)
215) Index for Case Management Job Aids (1 page)
216) Physician Job Aids (26 pages)
217) Case Receipt Job Aids (41 pages)
218) FDA letter dated March 17, 2010 re: reanalysis of Elitek study TDU4730 (4 pages)

ATTACHMENTS

1) FDA 482, Notice of Inspection, issued April 6, 2010
2) FDA 483, Inspectional Observations, issued May 13, 2009 (4 pages)
3) HFD-332 assignment memo dated March 9, 2010 (24 pages)
4) HFD-332 addendum to assignment dated April 8, 2010 (58 pages)
5) sanofi-aventis NDA, ANDA Product Listing (6 pages)
6) FDA letter dated October 16, 2009 Supplement Approval for Elitek (6 pages)
7) FDA letter dated January 9, 2004 Supplement Approval for Eloxatin for Injection, NDA 21-492 (5 pages)
8) FDA letter dated August 9, 2002 NDA Approval for Eloxatin for Injection, NDA 21-492 (5 pages)

D. Jeanne Denes

D. Jeanne Denes, Investigator